



## THE HEART IN RASOPATHIES

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## THE HEART IN RASOPATHIES

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60**ABSTRACT**

The cardiovascular phenotype associated with RASopathies has expanded far beyond the original descriptions of pulmonary valve stenosis by Dr. Jaqueline Noonan in 1968 and hypertrophic cardiomyopathy by Hirsch *et al* in 1975. Because of the common underlying RAS/MAPK pathway dysregulation, RASopathy syndromes usually present with a typical spectrum of overlapping cardiovascular anomalies, although less common cardiac defects can occur. The identification of the causative genetic variants has enabled the recognition of specific correlations between genotype and cardiac phenotype. Characterization and understanding of genotype–phenotype associations is not only important for counselling a family of an infant with a new diagnosis of a RASopathy condition but is also critical for their clinical prognosis with respect to cardiac disease, neurodevelopment and other organ system involvement over the lifetime of the patient.

This review will focus on the cardiac manifestations of the most common RASopathy syndromes, the relationship between cardiac defects and causal genetic variation, the contribution of cardiovascular abnormalities to morbidity and mortality and the most relevant follow-up issues for patients affected by RAS/MAPK pathway diseases, with respect to cardiac clinical outcomes and management, in children and in the adult population.

**KEYWORDS**

RASopathy, Congenital heart disease, Hypertrophic cardiomyopathy, Noonan syndrome, Cardio-facio-cutaneous syndrome, Costello syndrome, Noonan syndrome with multiple lentiginos.

## 63 INTRODUCTION

64  
65 Congenital heart defects (CHDs) and hypertrophic cardiomyopathy (HCM) are common  
66 features in RASopathies, with a prevalence from 60 to 90% in affected patients, as previously  
67 reported by several studies (Calcagni et al., 2020; Jhang et al., 2016; Lin et al., 2011; Linglart &  
68 Gelb, 2020; Prendiville et al., 2014).

69 As for other genetic syndromes, the presence of a cardiac disease can be the clinical finding  
70 that leads to the diagnosis, and RASopathies should always be considered in the differential  
71 diagnosis of children with HCM, in particular when other systemic or cardiac features of these traits  
72 are present (*e.g.*, short stature, hypertelorism, cryptorchidism, pulmonary valve stenosis)  
73 (Limongelli et al., 2020).

74 The prenatal recognition of some cardiac defects (*e.g.*, pulmonary valve stenosis and/or  
75 HCM), especially when associated with certain specific ultrasound findings, such as increased  
76 nuchal translucency or nuchal fold, polyhydramnios, cystic hygroma, hydrops fetalis,  
77 ascites/thoracic effusion or lymphatic dysplasia, can help to guide the differential diagnosis of  
78 RASopathies and define the indication for molecular genetic testing (Digilio et al., 2011; Myers et  
79 al., 2014; Scott et al., 2021).

80 In general, all patients should undergo a thorough cardiac assessment after the diagnosis,  
81 including ECG and two-dimensional color Doppler echocardiography, followed by regular cardiac  
82 surveillance based on the cardiac phenotype and on the specific genetic cause (Linglart & Gelb,  
83 2020).

84 This review will focus on: (a) the cardiac manifestations of the most common RASopathy  
85 syndromes, (b) the relationship between cardiac defects and causal genetic variation, (c) the  
86 contribution of cardiovascular abnormalities to morbidity and mortality and (d) the most relevant  
87 follow-up issues for patients affected by RAS/MAPK pathway diseases, with respect to cardiac  
88 clinical outcomes and management, in children and in the adult population.

## 1. CONGENITAL HEART DEFECTS IN RASOPATHIES

### *1.1 Cardiovascular anomalies and genotype-phenotype correlation*

RASopathy syndromes are a heterogeneous group of genetic multisystemic disorders caused by germline mutations in genes that encode proteins of the RAS/MAPK signal transduction pathway. Because of the common underlying RAS/MAPK pathway dysregulation, these syndromes have overlapping cardiac features and usually present with a typical spectrum of CHDs (Aoki et al., 2016; Rauen, 2013; Tartaglia & Gelb, 2010).

Among RASopathies, the most common syndromes are Noonan syndrome (OMIM PS163950), cardio-facio-cutaneous syndrome (CFCS, OMIM #115150), Costello syndrome (OMIM #218040), and Noonan syndrome with multiple lentigines (NSML, OMIM #151100).

The most common CHDs shown to be associated with these RASopathies include pulmonary valve stenosis (PVS), atrioventricular septal defect (AVSD) and atrial septal defect (ASD) (Calcagni et al., 2017; Digilio et al., 2013; Linglart & Gelb, 2020).

PVS represents the most recurrent CHD, reported in about 50% of individuals affected by Noonan syndrome (Bell et al., 2021; Roberts et al., 2013). The stenotic PV often has typical anatomic features, showing a dysplastic phenotype with myxomatous thickening and poorly mobile leaflets, resulting in severe right ventricular outflow tract obstruction. In some cases, PVS is supra-annular, with fusion of valvular cusps with the wall of the pulmonary artery (Digilio et al., 2009). In this regard, a thorough echocardiographic assessment of the site of obstruction and valvular morphology is fundamental to choose the optimal type of repair between balloon valvuloplasty and surgical treatment (Lin et al., 2008; McCrindle, 1994; Prendiville et al., 2014).

The reported prevalence of PVS in CFCS is ranging from 31% to 44% based on different cohorts (Allanson et al., 2011; Lin et al., 2011; Pierpont et al., 2014; Rodriguez-Viciano et al., 2006). In Costello syndrome, PVS is present in 15-20% of cases, associated with sub-valvular and supravalvular pulmonary stenosis. PVS may frequently be the result of sub-pulmonary muscular obstruction related to HCM. Rarely, severe forms of sub-valvular pulmonary stenosis have been described as “double-chambered right ventricle” (Gripp et al., 2019; Lin et al., 2011). Compared to other RASopathies, patients with Costello syndrome are less likely to have a severe form of PVS (Lin et al., 2011). Similarly, PVS in NSML is rare, mostly associated with HCM (Sarkozy et al., 2008).

AVSD represents a relatively common feature in Noonan syndrome with prevalence of about 15% (Linglart & Gelb, 2020; Marino et al., 1999), most frequently reported as partial AVSD

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3 125 and more rarely as complete AVSD (Digilio et al., 2013; Pradhan et al., 2013). AVSD in Noonan  
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5 126 syndrome may be associated with other cardiac defects including subaortic stenosis, structural  
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7 127 mitral valve (MV) anomalies, PVS and HCM (Digilio et al., 2013; Marino et al., 1995, 1999;  
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9 128 Pradhan et al., 2013).

10 129 In patients with Noonan syndrome, left-sided obstructive cardiac lesions have also been  
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12 130 reported in the absence of HCM spectrum. In particular, anatomic obstructions have been described  
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14 131 at valvular or sub-valvular level (Burch et al., 1993), in subaortic location, as a result of left  
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16 132 ventricular valve anomalies (Marino et al., 1995) or as coarctation of the aorta (CoA) (Digilio et al.,  
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18 133 1997, 1998). Data on the prevalence of left-sided obstructions in Noonan syndrome vary widely in  
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20 134 the different reported cohorts, ranging from 2% to 12.5% for CoA and 2% to 17% for left-sided  
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22 135 valve abnormalities (Colquitt & Noonan, 2014; Digilio et al., 1998; Digilio & Marino, 2001;  
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24 136 Prendiville et al., 2014).

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26 137 In addition, atypical CHD have been described, also as isolated cardiovascular lesions  
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28 138 (Calcagni et al., 2020; Leoni et al., 2022; Linglart & Gelb, 2020), including mitral and aortic valve  
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30 139 dysfunction, abnormalities of ascending and descending aorta, coronary artery dilation, enlargement  
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32 140 of the left atrial appendage and isolated pulmonary branches diseases. MV abnormalities most  
33  
34 141 frequently occur as a minor valvular dysfunction without clinical relevance, due to redundant MV  
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36 142 leaflets and/or elongated chords (Leoni et al., 2022). However, moderate-to-severe regurgitation can  
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38 143 also occur, in case of dysplastic leaflets and/or significant MV prolapse (Calcagni et al., 2020;  
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40 144 Linglart & Gelb, 2020). Since MV abnormalities might present as isolated valve disorder,  
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42 145 specifically without concomitant HCM, this raises the concern that RAS/MAPK pathway  
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44 146 dysregulation may independently affect the morphogenesis of the MV apparatus.

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46 147 Since 2001 when *PTPN11* gene missense mutations were found to be causative of Noonan  
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48 148 syndrome (Tartaglia et al., 2001), several studies have described the association between mutations  
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50 149 in genes encoding components of the RAS/MAPK signalling pathway and RASopathies (Aoki et  
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52 150 al., 2016). Congenital heart anomalies occur with different frequency among RASopathy  
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54 151 syndromes as a result of mutations in different genes, making it possible to delineate specific  
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56 152 correlations between genotype and cardiac phenotype.

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58 153 PVS is the most frequent cardiovascular defect in patients with Noonan syndrome due to  
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60 154 variants of *PTPN11*, with an approximate prevalence of 70% (Calcagni et al., 2017; Digilio et al.,  
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62 155 2010; Prendiville et al., 2014); specifically, an association between PVS and mutation on codon 308  
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64 156 of the gene has been recognized (Sarkozy et al., 2003; Tartaglia et al., 2002). In these patients, a  
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66 157 high prevalence of a severe form of pulmonary stenosis, both at valvular and supra-valvular levels  
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68 158 and in association with dysplastic PV, has been described (Leoni et al., 2022). Atrial septal defect

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3 159 (ASD), isolated or in association with PVS, is commonly detected in individuals with Noonan  
4 syndrome-*PTPN11* abnormalities, with a specific correlation of mutations on exon 3 of the gene  
5 160 (Sarkozy et al., 2003). Hemodynamically significant MV anomalies and AVSD can also be  
6 161 observed in patients with *PTPN11* variants, whereas tetralogy of Fallot, ventricular septal defect,  
7 162 patent ductus arteriosus and left-sided obstructions are less frequently reported (Digilio et al., 2013;  
8 163 Leoni et al., 2022; Marino et al., 1995; Prendiville et al., 2014). Conversely, *PTPN11* mutations on  
9 164 exon 7, 12 and 13 are associated with a small subset of CHDs in patients with NSML (Kauffman et  
10 165 al., 2021; Sarkozy et al., 2003). *PTPN11* is the most commonly mutated gene in patients with  
11 166 RASopathies and atypical CHD, such as aortic insufficiency, coronary artery dilation (particularly  
12 167 in patients with NSML), left atrial appendage dilatation and isolated pulmonary arteries anomalies  
13 168 (Calcagni et al., 2020).

14 169  
15 170 Among patients with *SOS1* variants, PVS of mild degree, often associated with ASD, is the  
16 171 most commonly described cardiac abnormality, followed by different types of valve diseases (Leoni  
17 172 et al., 2022; Roberts et al., 2007; Tartaglia et al., 2007). The cardiac phenotype associated with  
18 173 *SOS2* pathogenic variants is similar to the one described in association with *SOS1*, with pulmonary  
19 174 stenosis and septal defects being the most recurrent diseases (Cordeddu et al., 2015; Yamamoto et  
20 175 al., 2015). In individuals harboring pathogenic variants in *KRAS*, the heart is involved in the  
21 176 majority of cases without correlation with a specific cardiac phenotype, even though PVS seems to  
22 177 have a slightly greater prevalence over the other cardiac defects (Leoni et al., 2022; Pierpont &  
23 178 Digilio, 2018). In the subgroup of subjects with causal variation in *RAF1*, CHDs are poorly  
24 179 represented, with PVS and ASD being the most common defects (Kobayashi et al., 2010; Pandit et  
25 180 al., 2007; Razzaque et al., 2007). The prevalence of cardiovascular involvement in individuals  
26 181 harboring *RIT1* alleles ranges between 90 and 100%, with a strong correlation with PVS (Aoki et  
27 182 al., 2013; Yaoita et al., 2016). *LZTR1* cardiac phenotype includes different types of CHDs, most  
28 183 often ASD and PVS (Chinton et al., 2020; Umeki et al., 2019; Yamamoto et al., 2015).

29 184 Noonan syndrome with loose anagen hair (NSLAH) due to *SHOC2* gene variants seems to  
30 185 have correlation with PVS, MV dysplasia and septal defects (Cordeddu et al., 2009; Komatsuzaki et  
31 186 al., 2010). Less than half of patients with *HRAS* pathogenic variants, which underlie Costello  
32 187 syndrome, shows CHDs, particularly PVS and MV anomalies, mostly in association with HCM  
33 188 (Lin et al., 2011). Finally, the most frequent CHD in CFCS caused by *BRAF*, *MAP2K1* and  
34 189 *MAP2K2* variants is PVS, followed by ASD (Allanson et al., 2011; Armour & Allanson, 2007;  
35 190 Yaoita et al., 2016).

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3 191 Although many correlations between genetic variants and CHDs have been established,  
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5 192 others may not have emerged due to the small patient numbers, indicating that further research is  
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7 193 needed.

### 8 194 9 10 195 *1.2 Management options and outcome*

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14 197 The management of CHDs in RASopathies depends on the nature of the specific heart defect  
15 198 (**Figure 1**). However, when considering cardiac outcomes and necessities during the follow-up  
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17 199 period, cardiac defects can vary in terms of spectrum and severity, and consequently, their clinical  
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19 200 involvement is quite heterogeneous.

20 201 In Noonan syndrome, PVS shows differing degrees of severity: mild in ~60% of patients,  
21 202 moderate in ~10% and severe in ~30% (Colquitt & Noonan, 2014; Shaw et al., 2007). Usually, the  
22 203 mild form of PVS is nonprogressive and is unlikely to require intervention (Colquitt & Noonan,  
23 204 2014). Conversely, moderate-to-severe stenosis carries a higher rate of intervention, as a  
24 205 consequence of a higher degree of dysplasia of the valve leaflets. Patients with severe PVS very  
25 206 often undergo therapeutic procedure, often within two years of the diagnosis. Due to the distinct  
26 207 anatomic features of the pulmonary valve, the standard approach using percutaneous balloon  
27 208 valvuloplasty has been showed to be rarely successful in these patients (Linglart & Gelb, 2020),  
28 209 who need to undergo percutaneous re-intervention or surgical treatment (either valvotomy or valve  
29 210 leaflet excisions) (Hemmati et al., 2019; Lin et al., 2008; McCrindle, 1994; Prendiville et al., 2014).  
30 211 In 2018, Holzmann and colleagues reported their results concerning the immediate response to  
31 212 primary balloon pulmonary valvuloplasty. These results appeared sub-optimal in terms of reduction  
32 213 of right ventricle-pulmonary artery gradient with a higher reintervention rate when compared to  
33 214 non-syndromic patients (Holzmann et al., 2018). Therefore, with regard to risk of re-operation, a  
34 215 second procedure is frequently required, mostly due to the reoccurrence of PVS (Burch et al., 1993;  
35 216 Calcagni et al., 2017). Except for severe forms of PVS or PVS associated with other CHDs, the  
36 217 limited data available in literature on cardiac surgical prognosis in Noonan syndrome report that the  
37 218 early postoperative outcomes for these patients with PVS are comparable to those of non-syndromic  
38 219 patients (Hemmati et al., 2019).

39 220 Patients with AVSD frequently require an earlier intervention compared to individuals with  
40 221 Noonan syndrome affected by other cardiac anomalies (Calcagni et al., 2017). The concurrence of  
41 222 MV and/or aortic valve abnormalities in patients with AVSD results in a more complex and severe  
42 223 cardiac phenotype, deserving a careful evaluation for a more appropriate surgical approach  
43 224 (Calcagni et al., 2017).

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3 225 Left-sided obstructive cardiac lesions usually require surgical treatment. Indications for  
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5 226 intervention and surgical results vary widely and depend on the severity of the stenosis, the  
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7 227 presence of multilevel left heart obstruction, other associated cardiac lesions or other non-cardiac  
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9 228 risk factors. There is evidence that structural abnormalities of the MV may not only contribute to  
10 229 the development of a subaortic gradient in patients with obstructive HCM and mild septal  
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12 230 hypertrophy but might also affect the surgical outcome in patients with CHDs (Calcagni et al.,  
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14 231 2017). Another risk factor for morbidity and mortality is the occurrence of subaortic stenosis,  
15 232 probably due to the presence of accessory fibrous connective tissue and/or anomalous MV insertion  
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17 233 or abnormality of the left ventricular papillary muscles (Digilio et al., 1998; Marino et al., 1995).

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19 234 Among atypical CHD, increased awareness of the significance of MV anomalies has  
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21 235 ensured that MV morphology and function are carefully investigated for their possible clinical  
22 236 relevance, allowing an early detection of valvular dysfunction. Interestingly, recent studies  
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24 237 highlighted the concomitance of congenital dysplasia of two or more cardiac valves, described as  
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26 238 “congenital polyvalvular disease”, suggesting a new distinct cardiovascular phenotype of the  
27 239 RASopathies, with implications for diagnosis and management (Leoni et al., 2022; Matalon et al.,  
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29 240 2021). All these data raise the concern that also atypical CHD need to be carefully investigated and  
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31 241 continuously monitored for their possible impact on the clinical outcome (Calcagni et al., 2020;  
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33 242 Romano et al., 2010; Wolf et al., 2022). Most frequently, cardiac surgery is not required, as minor  
34 243 CHDs have often a favorable outcome (Calcagni et al., 2020). However, when a minor lesion is  
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36 244 associated to major cardiac defects, the latter will direct the need for intervention and the short-term  
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38 245 and long-term outcomes.

39 246 Overall mortality in patients with RASopathies is low, being less than 2.5% in the overall  
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41 247 population and less than 3% in the subgroup with cardiac disease, with flat survival curves  
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43 248 (Calcagni et al., 2017). Linglart and Gelb found a similar length of hospital stay comparing patients  
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45 249 with and without an associated syndrome (Linglart & Gelb, 2020). With respect to mortality, the  
46 250 adverse event generally occurs in the first two years of life, or during the adulthood. Overall  
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48 251 mortality in the atypical CHD subgroup is reduced when compared to typical cardiac diseases.

49 252 For adults with RASopathies, clear evidence is still lacking in the current literature.  
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51 253 Nonetheless, a previous study by Pierpont and Digilio highly recommended close follow-up for  
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53 254 such patients (Pierpont & Digilio, 2018). In their adult cohort, almost one-half needed cardiac  
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55 255 surgery and almost 3.5% experienced an arrhythmic event. In patients with PVS, long term sequelae  
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57 256 of chronic pulmonary regurgitation might be expected after surgical or catheter intervention. Even  
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59 257 in the absence of specific data in literature, the management of these patients should be similar to  
60 258 non-syndromic ones, needing pulmonary reevaluation later in life, when patients become

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3 259 symptomatic or when progressive RV dilatation or dysfunction occurs (Baumgartner et al., 2021;  
4 Stout et al., 2019). Although cardiac complications are common findings in the adult population,  
5 260 these heart diseases are usually stable and non-progressive after the surgical procedure (Smpokou et  
6 261 al., 2012).  
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10 263 Some adults with RASopathies were rarely found to have cardiac abnormalities other than  
11 structural CHDs, such as aortic root aneurysm, dilation of the ascending aorta, aortic dissection and  
12 264 giant aneurysms of the sinuses of Valsalva, in particular in Noonan syndrome patients with *PTPN11*  
13 265 mutations (Morgan et al., 1989; Power et al., 2006; Purnell et al., 2005; Shachter et al., 1984). In a  
14 266 retrospective study, Cornwall et al reported that aortic root aneurysms (defined as z-score  $\geq 2$ ) were  
15 267 prevalent in Noonan syndrome patients (~20%), often presenting during childhood, detected by  
16 268 routine screening and progressing over time (Cornwall et al., 2014). These findings imply that some  
17 269 individuals with Noonan syndrome may have connective tissue disorder-like vascular changes in  
18 270 adulthood, suggesting that all adults with Noonan syndrome should have lifelong cardiac follow-up.  
19 271

20 272 Coronary artery dilation, either isolated or with HCM, has also been reported in patients  
21 273 with RASopathies (Calcagni et al., 2016, 2020; Pacileo et al., 2006). In the setting of HCM,  
22 274 coronary artery ectasia likely reflects the consequences of increased myocardial mass, left ventricle  
23 275 outflow tract obstruction and diastolic dysfunction (Limongelli et al., 2007). Conversely, in patients  
24 276 without HCM or any other coexistent cardiovascular defects, coronary artery ectasia could be  
25 277 related to the RAS-MAPK system dysregulation itself (Calcagni et al., 2020). Although the clinical  
26 278 significance and long-term outcome of this finding remain to be clarified, clinicians should be  
27 279 aware of the increased cardiovascular risk in these patients, and careful coronary multimodality  
28 280 imaging, including coronary CT angiography or MRI angiography, is mandatory to monitor  
29 281 whether this anomaly may progress. Especially in adulthood, it is essential to prevent risk factors  
30 282 for myocardial infarction, such as systemic hypertension and hypercholesterolemia, which could  
31 283 accelerate atherosclerotic coronary artery disease. In such cases, use of antiplatelet or anticoagulant  
32 284 to prevent coronary artery thrombosis might be considered.  
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34 286 Of note, non-cardiac comorbidities may influence the cardiac surgery outcome, such as  
35 287 lymphatic abnormalities resulting in chylothorax in up to 10% (Hemmati et al., 2019) and bleeding  
36 288 diathesis, widely ranging in prevalence from 50% to 89% when considering either a history of  
37 289 bleeding and/or abnormal hemostatic lab results (Briggs & Dickerman, 2012; Artoni et al., 2014).  
38 290 Indeed, a wide spectrum of bleeding abnormalities including coagulation factor deficiency and  
39 291 platelet dysfunction has been described in patients with RASopathies, leading to possible bleeding  
40 292 complications during and after surgical procedures (Di Candia et al., 2021; Ruiz-Llobet et al.,  
41 293 2020). Thus, it is essential to investigate the coagulation system in these patients.

## 2. HYPERTROPHIC CARDIOMYOPATHY IN RASOPATHIES

### 2.1 Cardiovascular anomalies and genotype-phenotype correlation

In recent longitudinal cohorts of pediatric patients with HCM, RASopathies represent a common underlying etiology (approx. 20% of cases), with the highest prevalence of HCM in infancy (up to 42% of cases) (Alexander et al., 2018; Norrish et al., 2019) and a significant morbidity and mortality among affected individuals (Lioncino et al., 2022).

The occurrence of HCM is heterogeneous among the different RASopathies. The prevalence is highest in NSML, where HCM is diagnosed in up to 80% of patients, generally occurring during infancy (Limongelli et al., 2007). On the other hand, it occurs less frequently in the other RASopathies: 65% in Costello syndrome, 40% in CFCS, 20-25% in Noonan syndrome (Monda, Rubino, et al., 2021).

It has been suggested that the pathophysiology of HCM is related to a hyperactivation of the RAS-MAPK cascade, responsible for cardiomyocyte hypertrophy and myocardial disarray. However, this pathophysiological mechanism cannot be generalized to all RASopathies. For example, variants in *PTPN11* associated with Noonan syndrome are different from those related to NSML (Gelb & Tartaglia, 2011). While Noonan syndrome-related variants behave as a gain-of-function alleles with increased basal phosphatase activity (Keilhack et al., 2005), NSML-related variants are responsible for catalytic impairment (Lauriol & Kontaridis, 2011). Thus, in *PTPN11* Noonan syndrome-related variants the mechanism of HCM development is the upregulation of MAPK signaling, while *PTPN11* hypomorphic mutants associated with NSML cause enhanced signal flow through the PI3K-AKT-mTOR pathway. The elucidation of the pathophysiology of RASopathy-related HCM has significant clinical relevance for the possible development of targeted therapies.

### 2.2 Clinical features and diagnosis

HCM in RASopathies has higher risk of death and transplantation when compared to non-syndromic forms. When presenting below the 6 months of age with symptoms of heart failure, there is a higher risk of mortality, reaching early 22% at 1 year (6-fold higher than non-syndromic

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3 326 forms). While in surviving subjects without symptoms of heart failure, sudden cardiac death (SCD)  
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5 327 is more frequent among adolescents and young adults (Alexander et al., 2018).

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7 328 HCM in RASopathies is characterized by a more severe left ventricular hypertrophy (LVH)  
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9 329 and a higher prevalence and severity of left ventricular outflow tract obstruction (LVOTO)  
10 330 compared with non-syndromic forms (Cerrato et al., 2008). Several factors contribute to generating  
11  
12 331 LVOTO, including systolic anterior motion (SAM) of the MV, the displacement of papillary  
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14 332 muscles, the anomalous insertion of mitral chordae, and an accessory fibrous connective tissue that  
15 333 can cause subaortic stenosis. These complex mechanisms for LVOTO result in a high risk for  
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17 334 reintervention and death (Calcagni et al., 2017). Biventricular hypertrophy, due to the coexistence  
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19 335 of HCM and PVS, is relatively common and may represent a specific red flag for RASopathies  
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21 336 (Limongelli et al., 2020). Coronary artery abnormalities are commonly identified (up to 30%) and  
22 337 contribute to myocardial ischemia, worsening the imbalance between myocardial oxygen supply  
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24 338 and demand (Calcagni et al., 2020). In less than 6% of cases, MV abnormalities cause severe mitral  
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26 339 regurgitation, making more prone to symptoms for heart failure (Marino et al., 1995). Decreased  
27 340 height-for-age and lower left ventricular fractional shortening z-score are independent predictors of  
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29 341 mortality in patients with Noonan syndrome with HCM.

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31 342 Several ECG abnormalities have been reported, with signs of LVH and diffuse  
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33 343 repolarization abnormalities representing the most common findings. In addition, extreme right axis  
34 344 deviation (a “superior” QRS axis) represents a specific disease marker, commonly identified in  
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36 345 patients with Noonan syndrome with biventricular hypertrophy (Limongelli et al., 2020; Rapezzi et  
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38 346 al., 2013). Other ECG abnormalities that could be encountered are pseudo-infarction q waves and  
39 347 prolonged QT interval (Limongelli et al., 2008). Atrial tachyarrhythmias are commonly experienced  
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41 348 by patients with Costello syndrome (in more than 50%), but the natural history is usually benign,  
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43 349 with a high rate of responsiveness to medical therapy and spontaneous regression within the first  
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45 350 year of life (Levin et al., 2018). However, atrial tachycardia is not an exclusive feature of the  
46 351 Costello Syndrome (Lin et al., 2011). Non-reentrant atrial tachycardias (such as multifocal atrial  
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48 352 tachycardia and ectopic atrial tachycardia) have also been reported in patients with Noonan  
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50 353 syndrome (with *RAF1*, *SOS1* and *PTPN11* mutated genes). Furthermore, patients with mutation of  
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52 354 *PTPN11* gene in the spectrum of NSML may present with atrial disorders (Levin et al., 2018). Even  
53 355 rare, these atrial arrhythmias may appear in early infancy or in the first 1-2 months of life. These  
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55 356 forms present with a high ventricular rate and are often a challenge to be controlled by the medical  
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57 357 treatment.

58 358 Atrial tachycardia in RASopathy patients may occur in the presence or absence of HCM. In  
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60 359 addition, these atrial arrhythmias could cause tachycardia-induced cardiomyopathy with a reduced

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3 360 cardiac function or they may be a consequence of cardiomyopathy itself. Patients without HCM  
4 frequently experience a hyperdynamic left ventricle which probably may be related to the increased  
5 361 intracellular calcium. Disorders of intracellular calcium homeostasis have also been reported in  
6 362 RASopathies and may influence the management of antiarrhythmic therapy (Wehrens et al., 2004).  
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10 364 A recent study investigated the morphology of the ventricular septum determined by  
11 echocardiography, comparing patients with NSML and Noonan syndrome patients. In this study, a  
12 365 sigmoid septum and a ventricular septal bulge were observed predominantly in NSML patients,  
13 366 whereas biconvex septa were more common in Noonan syndrome patients. Furthermore, each  
14 367 cardiac phenotype showed association with specific genotypes and the clearest genotype-cardiac  
15 368 phenotype association occurred in patients carrying variants affecting specific exons of *PTPN11*  
16 (Kauffman et al., 2021). A more recent study confirmed the sigmoid-shaped ventricular septum  
17 369 morphology in a small subset of patients of its cohort of 116 cases, occurring in different  
18 370 RASopathies and associated with pathogenic variants involving multiple genes (Delogu et al.,  
19 371 2022). Whether ventricular septum morphology represents a distinct cardiac phenotype in  
20 372 RASopathies with correlations between echocardiographic features and the involved gene/variant  
21 373 remains to be addressed with further research.  
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24 376 The diagnostic algorithm for the diagnosis of HCM-related RASopathy is described in  
25 377 **Figure 2**. In summary, in patients fulfilling the diagnostic criteria for HCM (maximal left  
26 378 ventricular wall thickness  $\geq 15$  mm or  $\geq 13$  mm, without or with family history for HCM in adults,  
27 379 respectively, or  $\geq 2$  z-score in children), attention should be paid to identifying diagnostic clues  
28 380 suggestive for RASopathies (Authors/Task Force members et al., 2014; Limongelli et al., 2022;  
29 381 Ommen et al., 2020). In these patients, genetic testing for the identification of the disease-causing  
30 382 mutation is required for the diagnosis.  
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### 34 384 *2.3 Management options and outcomes*

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37 387 The diagnosis of HCM represents a major prognostic determinant in patients with  
38 388 RASopathies since the severity of the cardiac phenotype is associated with a low survival rate and  
39 389 high risk of death (Calcagni et al., 2017).

40 390 The risk for SCD appears to be significantly lower compared with patients with sarcomeric  
41 391 variants, but risk stratification for SCD in patients with RASopathies is challenging (Monda,  
42 392 Lioncino, Rubino, et al., 2022). In non-syndromic HCM, a previous history of sudden cardiac  
43 393 arrest, sustained or non-sustained ventricular tachycardia, unexplained syncope, and massive LVH  
44 394 have been suggested as risk factors for SCD, and in their presence, implantable cardioverter

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3 394 defibrillation (ICD) implantation may be considered (Monda, Lioncino, Rubino, et al., 2022;  
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5 395 Ommen et al., 2020). The relevance of these clinical features in RASopathy patients need to be  
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7 396 confirmed.

8 397 Medical therapy in patients with RASopathy-related HCM is mainly focused on managing  
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10 398 symptoms associated with LVOTO (Limongelli et al., 2022) (**Figure 3**). Non-vasodilating beta-  
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12 399 blockers represent the first line and should be titrated to the maximum tolerated dose to obtain a  
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14 400 LVOT gradient target <50 mmHg (i.e., the threshold for invasive strategy) (Authors/Task Force  
15 401 members et al., 2014; Monda, Lioncino, Palmiero, et al., 2022; Ommen et al., 2020). Non-  
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17 402 vasodilating calcium antagonists should be considered when beta-blockers are contraindicated or  
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19 403 not tolerated. However, their use should be carefully monitored since a rare association with severe  
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21 404 bradycardia or heart failure worsening in infants treated with verapamil has been reported (Moran  
22 405 & Colan, 1998). Disopyramide may be considered in addition to beta-blockers to reduce the degree  
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24 406 of obstruction and improve symptoms. This drug has proved to be effective also in Noonan  
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26 407 syndrome, but the magnitude of reduction should be tempered because the effect is temporary  
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28 408 (O'Connor et al., 2018). Surgical myectomy is the treatment of choice for patients with LVOTO  
29 409 who remain symptomatic despite optimal medical therapy. Patients with biventricular obstruction  
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31 410 with severe PVS usually manifest severe heart failure and symptoms refractory to medical therapy.  
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33 411 Pulmonary valvuloplasty is often ineffective in patients with RASopathies, and surgical repair is  
34 412 generally required.

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36 413 Orthotopic heart transplantation is rarely required in patients with RASopathies. It should be  
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38 414 considered in patients with severe heart failure and refractoriness to medical therapy, intractable  
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40 415 ventricular arrhythmias, cardiogenic shock requiring inotropes, severe diastolic dysfunction or in  
41 416 patients with severe LVOTO when surgical myectomy is not effective or feasible (Limongelli et al.,  
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43 417 2022; Monda, Lioncino, et al., 2021). The evaluation for indication to transplant should assess the  
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45 418 cardiac and non-cardiac risk (Gajarski et al., 2009). Knowledge of specific mutation should be of  
46 419 particular value in risk assessment: *PTPN11 p.Gln510Glu* mutation should be considered for an  
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48 420 earlier evaluation for transplant. Also, *PTPN11*- and *RIT1*-associated Noonan syndrome patients  
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50 421 have a known coagulopathy risk. Other mutations carry a higher risk for malignancies. This  
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52 422 information should be taken into account when assessing the individual risk prior to transplant  
53 423 listing. Growth issues and gastrostomy feeding are also commonly encountered in post-transplant  
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55 424 management (McCallen et al., 2019).

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57 425 Treatment of RASopathies with therapies targeting the RAS/MAPK cascade (in Noonan  
58 426 syndrome) or the PI3K/AKT/mTor pathway (in NSML) are limited to case reports suggesting a  
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60 427 beneficial effect of these therapeutic approaches in improving clinical status and resulting in LVH

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regression (Andelfinger et al., 2019; Marin et al., 2011; Nakano et al., 2022; Mussa et al., 2021). MEK inhibition, specifically, has also been reported as a treatment for arrhythmia and for lymphatic dysplasia, each of which can be isolated or comorbid conditions in children with RASopathies and cardiomyopathy, further supporting the efficacy of targeted therapy in RASopathy-associated conditions (Meisner et al., 2021; Dori et al., 2020; Nakano et al., 2022). However, the absence of clinical trials or large studies evaluating the risk and benefits of these drugs limits their use in clinical practice.

## CONCLUSIONS AND PERSPECTIVES

As this review demonstrates, the cardiovascular phenotype associated with RASopathies has expanded far beyond the original descriptions of pulmonary valve stenosis by Dr. Jacqueline Noonan in 1968 and hypertrophic cardiomyopathy by Hirsch *et al* in 1975 (Noonan, 1968; Hirsch et al., 1975). Yet, we still can appreciate the importance of these two cardiac findings with respect to disease burden and morbidity among individuals with RASopathy disorders. Our understanding of the phenotypes associated with RAS pathway gene variants has continued to expand at a rapid pace with a great deal of interest in the associated cardiovascular phenotypes based on the specific gene (Pierpont & Digilio, 2018). The common and overlapping cardiovascular phenotypes among all of the RASopathies underscores the recognized common pathophysiology of this group of conditions which generally speaking results in activating RAS/MAPK signal transduction. Still, there are clearly systemic—morphologic and other organ system—differences that are clear when one compares genotype groups. For example, patients with *PTPN11*-associated Noonan syndrome are distinguishable from patients with *RAF1*-associated Noonan syndrome, and their risk for cardiovascular disease also diverge slightly, with *PTPN11* conferring higher risk for pulmonary valve stenosis and less risk for hypertrophic cardiomyopathy, the converse being true for *RAF1*. Determination and understanding of genotype is not only important for counselling a family of an infant with a new diagnosis of a RASopathy condition but is also critical for their clinical prognosis with respect to cardiac disease, neurodevelopment and other organ system involvement over the lifetime of the patient.

Equally important is our better understanding of the prevalence of RASopathy disorders in patients with these common cardiac phenotypes, individually and in various combinations: pulmonary valve stenosis, infantile hypertrophic cardiomyopathy, polyvalvular dysplasia, and incidentally detected coronary artery ectasia. While pediatric cardiologists have, as a specialty, become quite knowledgeable about common syndromic forms of congenital heart disease and the relevance of genetic diagnosis in patients with certain types of congenital heart defects and



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3 462 cardiomyopathy, much more is still to be learned about how to use genetic diagnosis to improve  
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5 463 clinical outcomes. While barriers still exist to collecting genetic information from medical records  
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7 464 datasets, future research will depend on the ability to determine hospital and surgical outcomes  
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9 465 based on genetic etiology of diseases such as RASopathies. This data collection and analysis is  
10 466 necessary for understanding outcomes for individuals with RASopathies and providing evidence-  
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12 467 based precision care. Better understanding of new cardiovascular phenotypes is another area that  
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14 468 warrants further investigation. While treatments of pulmonary valve stenosis or hypertrophic  
15 469 cardiomyopathy are well studied, and clinical guidelines established, mildly dysplastic heart valves  
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17 470 and coronary ectasia/aneurysm attributable to RAS pathway variants are two examples of  
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19 471 cardiovascular disease for which there are no standards of care for monitoring or treatment. The  
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21 472 prevalence and associated morbidity of these findings is entirely unknown.

22 473 Efforts to improve our understanding of genotype-cardiac phenotype correlations in  
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24 474 RASopathies will be critical for optimal medical and surgical management. Genotype can for  
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26 475 example to some degree predict risk for associated bleeding disorders, lymphatic dysplasia,  
27 476 malignancy and other comorbidities that can have significant impact on outcome of a cardiac  
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29 477 procedure, and on quality of life for the individual. While the collective literature on RASopathies  
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31 478 and the associated cardiovascular features is expansive, large systematic population-based and long-  
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33 479 term outcomes research are lacking, and especially needed to truly understand how genotype can  
34 480 best inform clinical care in patients with RASopathy-associated cardiovascular disease. Of great  
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36 481 interest is the application of FDA-approved and investigational RAS/MAPK pathway inhibitors,  
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38 482 such as trametinib and sirolimus, in the treatment of hypertrophic cardiomyopathy and other morbid  
39 483 complications of RASopathies, such as lymphatic disease and malignancy. Understanding of the  
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41 484 influence of various gain-of function variants in the RAS/MAPK pathway will be critical to  
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43 485 understand the utility and efficacy of these treatments in children with Noonan syndrome and  
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45 486 related RASopathies. While only a handful of publications exist that describe isolated experiences  
46 487 with these pharmacologic agents, they are being used widely throughout the United States, Canada  
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48 488 and Europe under investigational/compassionate use or off-label. Real-world collection of this  
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50 489 collective experience is likely to shape the next decade of clinical research in RASopathy  
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52 490 conditions and will be a paradigm of personalized medicine for monogenic disease in the modern  
53 491 era.

## 57 493 **CONFLICT OF INTEREST**

58  
59 494  
60 495 The authors declare no conflict of interests.

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## DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

## REFERENCES

- Alexander, P. M. A., Nugent, A. W., Daubeney, P. E. F., Lee, K. J., Sleeper, L. A., Schuster, T., Turner, C., Davis, A. M., Semsarian, C., Colan, S. D., Robertson, T., Ramsay, J., Justo, R., Sholler, G. F., King, I., Weintraub, R. G., & National Australian Childhood Cardiomyopathy Study. (2018). Long-Term Outcomes of Hypertrophic Cardiomyopathy Diagnosed During Childhood: Results From a National Population-Based Study. *Circulation*, *138*(1), 29–36. <https://doi.org/10.1161/CIRCULATIONAHA.117.028895>
- Allanson, J. E., Annerén, G., Aoki, Y., Armour, C. M., Bondeson, M.-L., Cave, H., Gripp, K. W., Kerr, B., Nystrom, A.-M., Sol-Church, K., Verloes, A., & Zenker, M. (2011). Cardio-facio-cutaneous syndrome: Does genotype predict phenotype? *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics*, *157C*(2), 129–135. <https://doi.org/10.1002/ajmg.c.30295>
- Andelfinger, G., Marquis, C., Raboisson, M.-J., Théoret, Y., Waldmüller, S., Wiegand, G., Gelb, B. D., Zenker, M., Delrue, M.-A., & Hofbeck, M. (2019). Hypertrophic Cardiomyopathy in Noonan Syndrome Treated by MEK-Inhibition. *Journal of the American College of Cardiology*, *73*(17), 2237–2239. <https://doi.org/10.1016/j.jacc.2019.01.066>
- Aoki, Y., Niihori, T., Banjo, T., Okamoto, N., Mizuno, S., Kurosawa, K., Ogata, T., Takada, F., Yano, M., Ando, T., Hoshika, T., Barnett, C., Ohashi, H., Kawame, H., Hasegawa, T., Okutani, T., Nagashima, T., Hasegawa, S., Funayama, R., ... Matsubara, Y. (2013). Gain-of-Function Mutations in RIT1 Cause Noonan Syndrome, a RAS/MAPK Pathway Syndrome. *The American Journal of Human Genetics*, *93*(1), 173–180. <https://doi.org/10.1016/j.ajhg.2013.05.021>
- Aoki, Y., Niihori, T., Inoue, S., & Matsubara, Y. (2016). Recent advances in RASopathies. *Journal of Human Genetics*, *61*(1), 33–39. <https://doi.org/10.1038/jhg.2015.114>
- Armour, C. M., & Allanson, J. E. (2007). Further delineation of cardio-facio-cutaneous syndrome: Clinical features of 38 individuals with proven mutations. *Journal of Medical Genetics*, *45*(4), 249–254. <https://doi.org/10.1136/jmg.2007.054460>

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- 528 Artoni, A., Selicorni, A., Passamonti, S. M., Lecchi, A., Bucciarelli, P., Cerutti, M., Cianci, P.,  
529 Gianniello, F., & Martinelli, I. (2014). Hemostatic abnormalities in Noonan  
530 syndrome. *Pediatrics*, *133*(5), e1299–e1304. <https://doi.org/10.1542/peds.2013-3251>
- 531 Authors/Task Force members, Elliott, P. M., Anastasakis, A., Borger, M. A., Borggrefe, M.,  
532 Cecchi, F., Charron, P., Hagege, A. A., Lafont, A., Limongelli, G., Mahrholdt, H., McKenna, W. J.,  
533 Mogensen, J., Nihoyannopoulos, P., Nistri, S., Pieper, P. G., Pieske, B., Rapezzi, C., Rutten, F. H.,  
534 ... Watkins, H. (2014). 2014 ESC Guidelines on diagnosis and management of hypertrophic  
535 cardiomyopathy: The Task Force for the Diagnosis and Management of Hypertrophic  
536 Cardiomyopathy of the European Society of Cardiology (ESC). *European Heart Journal*, *35*(39),  
537 2733–2779. <https://doi.org/10.1093/eurheartj/ehu284>
- 538 Baumgartner, H., De Backer, J., Babu-Narayan, S. V., Budts, W., Chessa, M., Diller, G.-P., Lung,  
539 B., Kluin, J., Lang, I. M., Meijboom, F., Moons, P., Mulder, B. J. M., Oechslin, E., Roos-Hesselink,  
540 J. W., Schwerzmann, M., Sondergaard, L., Zeppenfeld, K., & ESC Scientific Document Group.  
541 (2021). 2020 ESC Guidelines for the management of adult congenital heart disease. *European*  
542 *Heart Journal*, *42*(6), 563–645. <https://doi.org/10.1093/eurheartj/ehaa554>
- 543 Bell, J. M., Considine, E. M., McCallen, L. M., & Chatfield, K. C. (2021). The Prevalence of  
544 Noonan Spectrum Disorders in Pediatric Patients with Pulmonary Valve Stenosis. *The Journal of*  
545 *Pediatrics*, *234*, 134-141.e5. <https://doi.org/10.1016/j.jpeds.2021.03.050>
- 546 Briggs, B. J., & Dickerman, J. D. (2012). Bleeding disorders in Noonan syndrome. *Pediatric blood*  
547 *& cancer*, *58*(2), 167–172. <https://doi.org/10.1002/pbc.23358>
- 548 Burch, M., Sharland, M., Shinebourne, E., Smith, G., Patton, M., & McKenna, W. (1993).  
549 Cardiologic abnormalities in Noonan syndrome: Phenotypic diagnosis and echocardiographic  
550 assessment of 118 patients. *Journal of the American College of Cardiology*, *22*(4), 1189–1192.  
551 [https://doi.org/10.1016/0735-1097\(93\)90436-5](https://doi.org/10.1016/0735-1097(93)90436-5)
- 552 Calcagni, G., Baban, A., De Luca, E., Leonardi, B., Pongiglione, G., & Digilio, M. C. (2016).  
553 Coronary artery ectasia in Noonan syndrome: Report of an individual with SOS1 mutation and  
554 literature review. *American Journal of Medical Genetics. Part A*, *170*(3), 665–669.  
555 <https://doi.org/10.1002/ajmg.a.37505>
- 556 Calcagni, G., Gagliostro, G., Limongelli, G., Unolt, M., De Luca, E., Digilio, M. C., Baban, A.,  
557 Albanese, S. B., Ferrero, G. B., Baldassarre, G., Agnoletti, G., Banaudi, E., Marek, J., Kaski, J. P.,  
558 Tuo, G., Marasini, M., Cairello, F., Madrigali, A., Pacileo, G., ... Versacci, P. (2020). Atypical

- 1  
2  
3 559 cardiac defects in patients with RASopathies: Updated data on CARNET study. *Birth Defects*  
4 *Research*, 112(10), 725–731. <https://doi.org/10.1002/bdr2.1670>  
5 560  
6  
7 561 Calcagni, G., Limongelli, G., D'Ambrosio, A., Gesualdo, F., Digilio, M. C., Baban, A., Albanese,  
8 S. B., Versacci, P., De Luca, E., Ferrero, G. B., Baldassarre, G., Agnoletti, G., Banaudi, E., Marek,  
9 562 J., Kaski, J. P., Tuo, G., Russo, M. G., Pacileo, G., Milanesi, O., ... Marino, B. (2017). Cardiac  
10 563 defects, morbidity and mortality in patients affected by RASopathies. CARNET study results.  
11 564 *International Journal of Cardiology*, 245, 92–98. <https://doi.org/10.1016/j.ijcard.2017.07.068>  
12 565  
13 566 Cerrato, F., Pacileo, G., Limongelli, G., Gagliardi, M. G., Santoro, G., Digilio, M. C., Di Salvo, G.,  
14 567 Ardorisio, R., Miele, T., & Calabrò, R. (2008). A standard echocardiographic and tissue Doppler  
15 568 study of morphological and functional findings in children with hypertrophic cardiomyopathy  
16 569 compared to those with left ventricular hypertrophy in the setting of Noonan and LEOPARD  
17 570 syndromes. *Cardiology in the Young*, 18(6), 575–580. <https://doi.org/10.1017/S104795110800320X>  
18 571  
19 572 Chinton, J., Huckstadt, V., Mucciolo, M., Lepri, F., Novelli, A., Gravina, L. P., & Obregon, M. G.  
20 573 (2020). Providing more evidence on *LZTR1* variants in Noonan syndrome patients. *American*  
21 574 *Journal of Medical Genetics Part A*, 182(2), 409–414. <https://doi.org/10.1002/ajmg.a.61445>  
22 575  
23 576 Colquitt, J. L., & Noonan, J. A. (2014). Cardiac findings in Noonan syndrome on long-term follow-  
24 577 up. *Congenital Heart Disease*, 9(2), 144–150. <https://doi.org/10.1111/chd.12102>  
25 578  
26 579 Cordeddu, V., Di Schiavi, E., Pennacchio, L. A., Ma'ayan, A., Sarkozy, A., Fodale, V., Cecchetti,  
27 580 S., Cardinale, A., Martin, J., Schackwitz, W., Lipzen, A., Zampino, G., Mazzanti, L., Digilio, M. C.,  
28 581 Martinelli, S., Flex, E., Lepri, F., Bartholdi, D., Kutsche, K., ... Tartaglia, M. (2009). Mutation of  
29 582 SHOC2 promotes aberrant protein N-myristoylation and causes Noonan-like syndrome with loose  
30 583 anagen hair. *Nature Genetics*, 41(9), 1022–1026. <https://doi.org/10.1038/ng.425>  
31 584  
32 585 Cordeddu, V., Yin, J. C., Gunnarsson, C., Virtanen, C., Drunat, S., Lepri, F., De Luca, A., Rossi,  
33 586 C., Ciolfi, A., Pugh, T. J., Bruselles, A., Priest, J. R., Pennacchio, L. A., Lu, Z., Danesh, A.,  
34 587 Quevedo, R., Hamid, A., Martinelli, S., Pantaleoni, F., ... Tartaglia, M. (2015). Activating  
35 588 Mutations Affecting the Dbl Homology Domain of SOS2 Cause Noonan Syndrome. *Human*  
36 589 *Mutation*, 36(11), 1080–1087. <https://doi.org/10.1002/humu.22834>  
37 590  
38 591 Cornwall, J. W., Green, R. S., Nielsen, J. C., & Gelb, B. D. (2014). Frequency of aortic dilation in  
39 592 Noonan syndrome. *The American Journal of Cardiology*, 113(2), 368–371.  
40 593 <https://doi.org/10.1016/j.amjcard.2013.09.034>  
41 594  
42 595  
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55  
56  
57  
58  
59  
60

589 Delogu, A. B., Blandino, R., Leoni, C., Tartaglia, M., & Zampino, G. (2022). RASopathies and  
590 sigmoid-shaped ventricular septum morphology: Evidence of a previously unappreciated cardiac  
591 phenotype. *Pediatric Research*. <https://doi.org/10.1038/s41390-022-02184-8>

592 Di Candia, F., Marchetti, V., Cirillo, F., Di Minno, A., Rosano, C., Pagano, S., Siano, M. A., Falco,  
593 M., Assunto, A., Boccia, G., Magliacane, G., Pinna, V., De Luca, A., Tartaglia, M., Di Minno, G.,  
594 Strisciuglio, P., & Melis, D. (2021). RASopathies and hemostatic abnormalities: key role of platelet  
595 dysfunction. *Orphanet journal of rare diseases*, *16*(1), 499. <https://doi.org/10.1186/s13023-021-02122-7>

597 Digilio, M. C., Lepri, F., Baban, A., Dentici, M. L., Versacci, P., Capolino, R., Ferese, R., De Luca,  
598 A., Tartaglia, M., Marino, B., & Dallapiccola, B. (2010). RASopathies: Clinical Diagnosis in the  
599 First Year of Life. *Molecular Syndromology*, *1*(6), 282–289. <https://doi.org/10.1159/000331266>

600 Digilio, M. C., Lepri, F., Baban, A., Dentici, M. L., Versacci, P., Capolino, R., Ferese, R., De Luca,  
601 A., Tartaglia, M., Marino, B., & Dallapiccola, B. (2011). RASopathies: Clinical Diagnosis in the  
602 First Year of Life. *Molecular Syndromology*, *1*(6), 282–289. <https://doi.org/10.1159/000331266>

603 Digilio, M. C., Marino, B., Giannotti, A., & Dallapiccola, B. (1997). Noonan syndrome with  
604 cardiac left-sided obstructive lesions. *Human Genetics*, *99*(2), 289.  
605 <https://doi.org/10.1007/s004390050357>

606 Digilio, M. C., Marino, B., Picchio, F., Prandstraller, D., Toscano, A., Giannotti, A., &  
607 Dallapiccola, B. (1998). Noonan syndrome and aortic coarctation. *American Journal of Medical  
608 Genetics*, *80*(2), 160–162.

609 Digilio, M. C., Marino, B., Sarkozy, A., Versacci, P., & Dallapiccola, B. (2009). The Heart in Ras-  
610 MAPK Pathway Disorders. *Noonan Syndrome and Related Disorders - A Matter of Deregulated  
611 Ras Signaling*, *17*, 109–118. <https://doi.org/10.1159/000164847>

612 Digilio, M. C., Romana Lepri, F., Dentici, M. L., Henderson, A., Baban, A., Roberti, M. C.,  
613 Capolino, R., Versacci, P., Surace, C., Angioni, A., Tartaglia, M., Marino, B., & Dallapiccola, B.  
614 (2013). Atrioventricular canal defect in patients with RASopathies. *European Journal of Human  
615 Genetics: EJHG*, *21*(2), 200–204. <https://doi.org/10.1038/ejhg.2012.145>

616 Digilio, M., & Marino, B. (2001). Clinical manifestations of Noonan syndrome. *Images in  
617 Paediatric Cardiology*, *3*(2), 19–30.

1

2

3 618 Dori, Y., Smith, C., Pinto, E., Snyder, K., March, M. E., Hakonarson, H., & Belasco, J. (2020).  
4  
5 619 Severe Lymphatic Disorder Resolved With MEK Inhibition in a Patient With Noonan Syndrome  
6  
7 620 and SOS1 Mutation. *Pediatrics*, *146*(6), e20200167. <https://doi.org/10.1542/peds.2020-0167>

8

9 621 Gajarski, R., Naftel, D. C., Pahl, E., Alejos, J., Pearce, F. B., Kirklin, J. K., Zamberlan, M.,  
10  
11 622 Dipchand, A. I., & Pediatric Heart Transplant Study Investigators. (2009). Outcomes of pediatric  
12  
13 623 patients with hypertrophic cardiomyopathy listed for transplant. *The Journal of Heart and Lung*  
14 624 *Transplantation: The Official Publication of the International Society for Heart Transplantation*,  
15  
16 625 *28*(12), 1329–1334. <https://doi.org/10.1016/j.healun.2009.05.028>

17

18 626 Gelb, B. D., & Tartaglia, M. (2011). RAS signaling pathway mutations and hypertrophic  
19  
20 627 cardiomyopathy: Getting into and out of the thick of it. *The Journal of Clinical Investigation*,  
21  
22 628 *121*(3), 844–847. <https://doi.org/10.1172/JCI46399>

23

24 629 Gripp, K. W., Morse, L. A., Axelrad, M., Chatfield, K. C., Chidekel, A., Dobyns, W., Doyle, D.,  
25  
26 630 Kerr, B., Lin, A. E., Schwartz, D. D., Sibbles, B. J., Siegel, D., Shankar, S. P., Stevenson, D. A.,  
27  
28 631 Thacker, M. M., Weaver, K. N., White, S. M., & Rauen, K. A. (2019). Costello syndrome: Clinical  
29  
30 632 phenotype, genotype, and management guidelines. *American Journal of Medical Genetics, Part A*,  
31 633 *179*(9), 1725–1744. <https://doi.org/10.1002/ajmg.a.61270>

32

33 634 Hemmati, P., Dearani, J. A., Daly, R. C., King, K. S., Ammash, N. M., Cetta, F., & Schaff, H. V.  
34  
35 635 (2019). Early Outcomes of Cardiac Surgery in Patients with Noonan Syndrome. *Seminars in*  
36  
37 636 *Thoracic and Cardiovascular Surgery*, *31*(3), 507–513.  
38  
39 637 <https://doi.org/10.1053/j.semtcvs.2018.12.004>

40

41 638 Hirsch, H. D., Gelband, H., Garcia, O., Gottlieb, S., & Tamer, D. M. (1975). Rapidly progressive  
42  
43 639 obstructive cardiomyopathy in infants with Noonan's syndrome. Report of two  
44  
45 640 cases. *Circulation*, *52*(6), 1161–1165. <https://doi.org/10.1161/01.cir.52.6.1161>

46

47 641 Holzmann, J., Tibby, S. M., Rosenthal, E., Qureshi, S., Morgan, G., & Krasemann, T. (2018).  
48  
49 642 Results of balloon pulmonary valvoplasty in children with Noonan's syndrome. *Cardiology in the*  
50  
51 643 *young*, *28*(5), 647–652. <https://doi.org/10.1017/S1047951117002827>

52

53 644 Jhang, W. K., Choi, J.-H., Lee, B. H., Kim, G.-H., & Yoo, H.-W. (2016). Cardiac Manifestations  
54  
55 645 and Associations with Gene Mutations in Patients Diagnosed with RASopathies. *Pediatric*  
56 646 *Cardiology*, *37*(8), 1539–1547. <https://doi.org/10.1007/s00246-016-1468-6>

57

58 647 Kauffman, H., Ahrens-Nicklas, R. C., Calderon-Anyosa, R. J. C., Ritter, A. L., Lin, K. Y., Rossano,  
59  
60 648 J. W., Quartermain, M. D., & Banerjee, A. (2021). Genotype-phenotype association by

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
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55  
56  
57  
58  
59  
60

649 echocardiography offers incremental value in patients with Noonan Syndrome with Multiple  
650 Lentigines. *Pediatric Research*, 90(2), 444–451. <https://doi.org/10.1038/s41390-020-01292-7>

651 Keilhack, H., David, F. S., McGregor, M., Cantley, L. C., & Neel, B. G. (2005). Diverse  
652 biochemical properties of Shp2 mutants. Implications for disease phenotypes. *The Journal of*  
653 *Biological Chemistry*, 280(35), 30984–30993. <https://doi.org/10.1074/jbc.M504699200>

654 Kobayashi, T., Aoki, Y., Niihori, T., Cavé, H., Verloes, A., Okamoto, N., Kawame, H., Fujiwara, I.,  
655 Takada, F., Ohata, T., Sakazume, S., Ando, T., Nakagawa, N., Lapunzina, P., Meneses, A. G.,  
656 Gillessen-Kaesbach, G., Wiczorek, D., Kurosawa, K., Mizuno, S., ... Matsubara, Y. (2010).  
657 Molecular and clinical analysis of *RAF1* in Noonan syndrome and related disorders:  
658 Dephosphorylation of serine 259 as the essential mechanism for mutant activation. *Human*  
659 *Mutation*, 31(3), 284–294. <https://doi.org/10.1002/humu.21187>

660 Komatsuzaki, S., Aoki, Y., Niihori, T., Okamoto, N., Hennekam, R. C. M., Hopman, S., Ohashi, H.,  
661 Mizuno, S., Watanabe, Y., Kamasaki, H., Kondo, I., Moriyama, N., Kurosawa, K., Kawame, H.,  
662 Okuyama, R., Imaizumi, M., Rikiishi, T., Tsuchiya, S., Kure, S., & Matsubara, Y. (2010). Mutation  
663 analysis of the SHOC2 gene in Noonan-like syndrome and in hematologic malignancies. *Journal of*  
664 *Human Genetics*, 55(12), 801–809. <https://doi.org/10.1038/jhg.2010.116>

665 Lauriol, J., & Kontaridis, M. I. (2011). PTPN11-associated mutations in the heart: Has LEOPARD  
666 changed Its RASpots? *Trends in Cardiovascular Medicine*, 21(4), 97–104.  
667 <https://doi.org/10.1016/j.tcm.2012.03.006>

668 Leoni, C., Blandino, R., Delogu, A. B., De Rosa, G., Onesimo, R., Verusio, V., Marino, M. V.,  
669 Lanza, G. A., Rigante, D., Tartaglia, M., & Zampino, G. (2022). Genotype-cardiac phenotype  
670 correlations in a large single-center cohort of patients affected by RASopathies: Clinical  
671 implications and literature review. *American Journal of Medical Genetics Part A*, 188(2), 431–445.  
672 <https://doi.org/10.1002/ajmg.a.62529>

673 Levin, M. D., Saitta, S. C., Gripp, K. W., Wenger, T. L., Ganesh, J., Kalish, J. M., Epstein, M. R.,  
674 Smith, R., Czosek, R. J., Ware, S. M., Goldenberg, P., Myers, A., Chatfield, K. C., Gillespie, M. J.,  
675 Zackai, E. H., & Lin, A. E. (2018). Nonreentrant atrial tachycardia occurs independently of  
676 hypertrophic cardiomyopathy in RASopathy patients. *American Journal of Medical Genetics. Part*  
677 *A*, 176(8), 1711–1722. <https://doi.org/10.1002/ajmg.a.38854>

678 Limongelli, G., Adorisio, R., Baggio, C., Bauce, B., Biagini, E., Castelletti, S., Favilli, S., Imazio,  
679 M., Lioncino, M., Merlo, M., Monda, E., Olivotto, I., Parisi, V., Pelliccia, F., Basso, C., Sinagra,

- 1  
2  
3 680 G., Indolfi, C., Autore, C., WG on Cardiomyopathies of SIC (Società Italiana di Cardiologia), &  
4  
5 681 WG on Cardiomyopathies of SICPed (Società Italiana di Cardiologia Pediatrica). (2022). Diagnosis  
6  
7 682 and Management of Rare Cardiomyopathies in Adult and Paediatric Patients. A Position Paper of  
8  
9 683 the Italian Society of Cardiology (SIC) and Italian Society of Paediatric Cardiology (SICP).  
10 684 *International Journal of Cardiology*, 357, 55–71. <https://doi.org/10.1016/j.ijcard.2022.03.050>  
11  
12 685 Limongelli, G., Monda, E., Tramonte, S., Gragnano, F., Masarone, D., Frisso, G., Esposito, A.,  
13  
14 686 Gravino, R., Ammendola, E., Salerno, G., Rubino, M., Caiazza, M., Russo, M., Calabrò, P., Elliott,  
15  
16 687 P. M., & Pacileo, G. (2020). Prevalence and clinical significance of red flags in patients with  
17  
18 688 hypertrophic cardiomyopathy. *International Journal of Cardiology*, 299, 186–191.  
19 689 <https://doi.org/10.1016/j.ijcard.2019.06.073>  
20  
21  
22 690 Limongelli, G., Pacileo, G., Marino, B., Digilio, M. C., Sarkozy, A., Elliott, P., Versacci, P.,  
23  
24 691 Calabro, P., De Zorzi, A., Di Salvo, G., Syrris, P., Patton, M., McKenna, W. J., Dallapiccola, B., &  
25 692 Calabro, R. (2007). Prevalence and clinical significance of cardiovascular abnormalities in patients  
26  
27 693 with the LEOPARD syndrome. *The American Journal of Cardiology*, 100(4), 736–741.  
28 694 <https://doi.org/10.1016/j.amjcard.2007.03.093>  
29  
30  
31 695 Limongelli, G., Sarkozy, A., Pacileo, G., Calabrò, P., Digilio, M. C., Maddaloni, V., Gagliardi, G.,  
32  
33 696 Di Salvo, G., Iacomino, M., Marino, B., Dallapiccola, B., & Calabrò, R. (2008). Genotype-  
34  
35 697 phenotype analysis and natural history of left ventricular hypertrophy in LEOPARD syndrome.  
36 698 *American Journal of Medical Genetics. Part A*, 146A(5), 620–628.  
37 699 <https://doi.org/10.1002/ajmg.a.32206>  
38  
39  
40 700 Lin, A. E., Alexander, M. E., Colan, S. D., Kerr, B., Rauen, K. A., Noonan, J., Baffa, J., Hopkins,  
41  
42 701 E., Sol-Church, K., Limongelli, G., Digilio, M. C., Marino, B., Innes, A. M., Aoki, Y., Silberbach,  
43  
44 702 M., Delrue, M.-A., White, S. M., Hamilton, R. M., O'Connor, W., ... Gripp, K. W. (2011). Clinical,  
45  
46 703 pathological, and molecular analyses of cardiovascular abnormalities in Costello syndrome: A  
47 704 Ras/MAPK pathway syndrome. *American Journal of Medical Genetics Part A*, 155(3), 486–507.  
48 705 <https://doi.org/10.1002/ajmg.a.33857>  
49  
50  
51 706 Lin, A. E., Basson, C. T., Goldmuntz, E., Magoulas, P. L., McDermott, D. A., McDonald-McGinn,  
52  
53 707 D. M., McPherson, E., Morris, C. A., Noonan, J., Nowak, C., Pierpont, M. E., Pyeritz, R. E., Rope,  
54  
55 708 A. F., Zackai, E., & Poer, B. R. (2008). Adults with genetic syndromes and cardiovascular  
56  
57 709 abnormalities: Clinical history and management. *Genetics in Medicine*, 10(7), 469–494.  
58 710 <https://doi.org/10.1097/GIM.0b013e3181772111>  
59  
60



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50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 711 Linglart, L., & Gelb, B. D. (2020). Congenital heart defects in Noonan syndrome: Diagnosis,  
712 management, and treatment. *American Journal of Medical Genetics. Part C, Seminars in Medical*  
713 *Genetics*, 184(1), 73–80. <https://doi.org/10.1002/ajmg.c.31765>
- 714 Lioncino, M., Monda, E., Verrillo, F., Moscarella, E., Calcagni, G., Drago, F., Marino, B., Digilio,  
715 M. C., Putotto, C., Calabrò, P., Russo, M. G., Roberts, A. E., Gelb, B. D., Tartaglia, M., &  
716 Limongelli, G. (2022). Hypertrophic Cardiomyopathy in RASopathies: Diagnosis, Clinical  
717 Characteristics, Prognostic Implications, and Management. *Heart Failure Clinics*, 18(1), 19–29.  
718 <https://doi.org/10.1016/j.hfc.2021.07.004>
- 719 Marin, T. M., Keith, K., Davies, B., Conner, D. A., Guha, P., Kalaitzidis, D., Wu, X., Lauriol, J.,  
720 Wang, B., Bauer, M., Bronson, R., Franchini, K. G., Neel, B. G., & Kontaridis, M. I. (2011).  
721 Rapamycin reverses hypertrophic cardiomyopathy in a mouse model of LEOPARD syndrome–  
722 associated PTPN11 mutation. *Journal of Clinical Investigation*, 121(3), 1026–1043.  
723 <https://doi.org/10.1172/JCI44972>
- 724 Marino, B., Digilio, M. C., Toscano, A., Giannotti, A., & Dallapiccola, B. (1999). Congenital heart  
725 diseases in children with Noonan syndrome: An expanded cardiac spectrum with high prevalence of  
726 atrioventricular canal. *The Journal of Pediatrics*, 135(6), 703–706. [https://doi.org/10.1016/s0022-3476\(99\)70088-0](https://doi.org/10.1016/s0022-3476(99)70088-0)
- 728 Marino, B., Gagliardi, M. G., Digilio, M. C., Polletta, B., Grazioli, S., Agostino, D., Giannotti, A.,  
729 & Dallapiccola, B. (1995). Noonan syndrome: Structural abnormalities of the mitral valve causing  
730 subaortic obstruction. *European Journal of Pediatrics*, 154(12), 949–952.  
731 <https://doi.org/10.1007/BF01958636>
- 732 Matalon, D. R., Stevenson, D. A., Bhoj, E. J., Santani, A. B., Keena, B., Cohen, M. S., Lin, A. E.,  
733 Sheppard, S. E., & Zackai, E. H. (2021). Congenital polyvalvular disease expands the cardiac  
734 phenotype of the RASopathies. *American Journal of Medical Genetics Part A*, 185(5), 1486–1493.  
735 <https://doi.org/10.1002/ajmg.a.62146>
- 736 McCallen, L. M., Ameduri, R. K., Denfield, S. W., Dodd, D. A., Everitt, M. D., Johnson, J. N., Lee,  
737 T. M., Lin, A. E., Lohr, J. L., May, L. J., Pierpont, M. E., Stevenson, D. A., & Chatfield, K. C.  
738 (2019). Cardiac transplantation in children with Noonan syndrome. *Pediatric Transplantation*,  
739 23(6), e13535. <https://doi.org/10.1111/petr.13535>

1  
2  
3  
4  
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48  
49  
50  
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52  
53  
54  
55  
56  
57  
58  
59  
60

- 740 McCrindle, B. W. (1994). Independent predictors of long-term results after balloon pulmonary  
741 valvuloplasty. Valvuloplasty and Angioplasty of Congenital Anomalies (VACA) Registry  
742 Investigators. *Circulation*, *89*(4), 1751–1759. <https://doi.org/10.1161/01.CIR.89.4.1751>
- 743 Meisner, J. K., Bradley, D. J., & Russell, M. W. (2021). Molecular Management of Multifocal  
744 Atrial Tachycardia in Noonan's Syndrome With MEK1/2 Inhibitor Trametinib. *Circulation.  
745 Genomic and precision medicine*, *14*(5), e003327. <https://doi.org/10.1161/CIRCGEN.121.003327>
- 746 Monda, E., Lioncino, M., Pacileo, R., Rubino, M., Cirillo, A., Fusco, A., Esposito, A., Verrillo, F.,  
747 Di Fraia, F., Mauriello, A., Tessitore, V., Caiazza, M., Cesaro, A., Calabrò, P., Russo, M. G., &  
748 Limongelli, G. (2021). Advanced Heart Failure in Special Population-Pediatric Age. *Heart Failure  
749 Clinics*, *17*(4), 673–683. <https://doi.org/10.1016/j.hfc.2021.05.011>
- 750 Monda, E., Lioncino, M., Palmiero, G., Franco, F., Rubino, M., Cirillo, A., Verrillo, F., Fusco, A.,  
751 Caiazza, M., Mazzella, M., Moscarella, E., Dongiglio, F., Sepe, J., Pacileo, G., Calabrò, P., &  
752 Limongelli, G. (2022). Bisoprolol for treatment of symptomatic patients with obstructive  
753 hypertrophic cardiomyopathy. The BASIC (bisoprolol AS therapy in hypertrophic cardiomyopathy)  
754 study. *International Journal of Cardiology*, *354*, 22–28.  
755 <https://doi.org/10.1016/j.ijcard.2022.03.013>
- 756 Monda, E., Lioncino, M., Rubino, M., Caiazza, M., Cirillo, A., Fusco, A., Pacileo, R., Fimiani, F.,  
757 Amodio, F., Borrelli, N., Colonna, D., D'Onofrio, B., Frisso, G., Drago, F., Castelletti, S., Sarubbi,  
758 B., Calabrò, P., Russo, M. G., & Limongelli, G. (2022). The Risk of Sudden Unexpected Cardiac  
759 Death in Children: Epidemiology, Clinical Causes, and Prevention. *Heart Failure Clinics*, *18*(1),  
760 115–123. <https://doi.org/10.1016/j.hfc.2021.07.002>
- 761 Monda, E., Rubino, M., Lioncino, M., Di Fraia, F., Pacileo, R., Verrillo, F., Cirillo, A., Caiazza, M.,  
762 Fusco, A., Esposito, A., Fimiani, F., Palmiero, G., Pacileo, G., Calabrò, P., Russo, M. G., &  
763 Limongelli, G. (2021). Hypertrophic Cardiomyopathy in Children: Pathophysiology, Diagnosis, and  
764 Treatment of Non-sarcomeric Causes. *Frontiers in Pediatrics*, *9*, 632293.  
765 <https://doi.org/10.3389/fped.2021.632293>
- 766 Moran, A. M., & Colan, S. D. (1998). Verapamil therapy in infants with hypertrophic  
767 cardiomyopathy. *Cardiology in the Young*, *8*(3), 310–319.  
768 <https://doi.org/10.1017/s1047951100006818>

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53  
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55  
56  
57  
58  
59  
60

- 769 Morgan, J. M., Coupe, M. O., Honey, M., & Miller, G. A. (1989). Aneurysms of the sinuses of  
770 Valsalva in Noonan's syndrome. *European Heart Journal*, *10*(2), 190–193.  
771 <https://doi.org/10.1093/oxfordjournals.eurheartj.a059462>
- 772 Mussa, A., Carli, D., Giorgio, E., Villar, A. M., Cardaropoli, S., Carbonara, C., Campagnoli, M. F.,  
773 Galletto, P., Palumbo, M., Olivieri, S., Isella, C., Andelfinger, G., Tartaglia, M., Botta, G., Brusco,  
774 A., Medico, E., & Ferrero, G. B. (2021). MEK Inhibition in a Newborn with *RAF1*-Associated  
775 Noonan Syndrome Ameliorates Hypertrophic Cardiomyopathy but Is Insufficient to Revert  
776 Pulmonary Vascular Disease. *Genes*, *13*(1), 6. <https://doi.org/10.3390/genes13010006>
- 777 Myers, A., Bernstein, J. A., Brennan, M.-L., Curry, C., Esplin, E. D., Fisher, J., Homeyer, M.,  
778 Manning, M. A., Muller, E. A., Niemi, A.-K., Seaver, L. H., Hintz, S. R., & Hudgins, L. (2014).  
779 Perinatal features of the RASopathies: Noonan syndrome, cardiofaciocutaneous syndrome and  
780 Costello syndrome. *American Journal of Medical Genetics. Part A*, *164A*(11), 2814–2821.  
781 <https://doi.org/10.1002/ajmg.a.36737>
- 782 Nakano, T. A., Rankin, A. W., Annam, A., Kulungowski, A. M., McCallen, L. M., Hill, L. R., &  
783 Chatfield, K. C. (2022). Trametinib for Refractory Chylous Effusions and Systemic Complications  
784 in Children with Noonan Syndrome. *The Journal of pediatrics*, S0022-3476(22)00479-6. Advance  
785 online publication. <https://doi.org/10.1016/j.jpeds.2022.05.030>
- 786 Noonan J. A. (1968). Hypertelorism with Turner phenotype. A new syndrome with associated  
787 congenital heart disease. *American journal of diseases of children* (1960), *116*(4), 373–380.  
788 <https://doi.org/10.1001/archpedi.1968.02100020377005>
- 789 Norrish, G., Field, E., Mcleod, K., Ilina, M., Stuart, G., Bhole, V., Uzun, O., Brown, E., Daubeney,  
790 P. E. F., Lota, A., Linter, K., Mathur, S., Bharucha, T., Kok, K. L., Adwani, S., Jones, C. B.,  
791 Reinhardt, Z., & Kaski, J. P. (2019). Clinical presentation and survival of childhood hypertrophic  
792 cardiomyopathy: A retrospective study in United Kingdom. *European Heart Journal*, *40*(12), 986–  
793 993. <https://doi.org/10.1093/eurheartj/ehy798>
- 794 O'Connor, M. J., Miller, K., Shaddy, R. E., Lin, K. Y., Hanna, B. D., Ravishankar, C., & Rossano,  
795 J. W. (2018). Disopyramide use in infants and children with hypertrophic cardiomyopathy.  
796 *Cardiology in the Young*, *28*(4), 530–535. <https://doi.org/10.1017/S1047951117002384>
- 797 Ommen, S. R., Mital, S., Burke, M. A., Day, S. M., Deswal, A., Elliott, P., Evanovich, L. L., Hung,  
798 J., Joglar, J. A., Kantor, P., Kimmelstiel, C., Kittleson, M., Link, M. S., Maron, M. S., Martinez, M.  
799 W., Miyake, C. Y., Schaff, H. V., Semsarian, C., & Sorajja, P. (2020). 2020 AHA/ACC Guideline

- 1  
2  
3 800 for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy: A Report of the  
4  
5 801 American College of Cardiology/American Heart Association Joint Committee on Clinical Practice  
6  
7 802 Guidelines. *Circulation*, *142*(25), e558–e631. <https://doi.org/10.1161/CIR.0000000000000937>  
8  
9 803 Pacileo, G., Calabrò, P., Limongelli, G., Santoro, G., Digilio, M., Sarkozy, A., Marino, B.,  
10  
11 804 Dallapiccola, B., & Calabrò, R. (2006). Diffuse coronary dilation in a young patient with  
12  
13 805 LEOPARD syndrome. *International Journal of Cardiology*, *112*(2), e35-37.  
14 806 <https://doi.org/10.1016/j.ijcard.2006.02.037>  
15  
16 807 Pandit, B., Sarkozy, A., Pennacchio, L. A., Carta, C., Oishi, K., Martinelli, S., Pogna, E. A.,  
17  
18 808 Schackwitz, W., Ustaszewska, A., Landstrom, A., Bos, J. M., Ommen, S. R., Esposito, G., Lepri,  
19  
20 809 F., Faul, C., Mundel, P., López Sigüero, J. P., Tenconi, R., Selicorni, A., ... Gelb, B. D. (2007).  
21  
22 810 Gain-of-function RAF1 mutations cause Noonan and LEOPARD syndromes with hypertrophic  
23  
24 811 cardiomyopathy. *Nature Genetics*, *39*(8), 1007–1012. <https://doi.org/10.1038/ng2073>  
25  
26 812 Pierpont, M. E., & Digilio, M. C. (2018). Cardiovascular disease in Noonan syndrome: *Current*  
27  
28 813 *Opinion in Pediatrics*, *30*(5), 601–608. <https://doi.org/10.1097/MOP.0000000000000669>  
29  
30 814 Pierpont, M. E. M., Magoulas, P. L., Adi, S., Kavamura, M. I., Neri, G., Noonan, J., Pierpont, E. I.,  
31  
32 815 Reinker, K., Roberts, A. E., Shankar, S., Sullivan, J., Wolford, M., Conger, B., Santa Cruz, M., &  
33  
34 816 Rauen, K. A. (2014). Cardio-facio-cutaneous syndrome: Clinical features, diagnosis, and  
35 817 management guidelines. *Pediatrics*, *134*(4), e1149-1162. <https://doi.org/10.1542/peds.2013-3189>  
36  
37 818 Power, P. D., Lewin, M. B., Hannibal, M. C., & Glass, I. A. (2006). Aortic root dilatation is a rare  
38 819 complication of Noonan syndrome. *Pediatric Cardiology*, *27*(4), 478–480.  
39  
40 820 <https://doi.org/10.1007/s00246-006-1210-x>  
41  
42  
43 821 Pradhan, A. K., Pandey, S., Usman, K., Kumar, M., & Mishra, R. (2013). Noonan syndrome with  
44  
45 822 complete atrioventricular canal defect with pulmonary stenosis. *Journal of the American College of*  
46  
47 823 *Cardiology*, *62*(20), 1905. <https://doi.org/10.1016/j.jacc.2013.06.062>  
48  
49 824 Prendiville, T. W., Gauvreau, K., Tworog-Dube, E., Patkin, L., Kucherlapati, R. S., Roberts, A. E.,  
50  
51 825 & Lacro, R. V. (2014). Cardiovascular disease in Noonan syndrome. *Archives of Disease in*  
52  
53 826 *Childhood*, *99*(7), 629–634. <https://doi.org/10.1136/archdischild-2013-305047>  
54  
55 827 Purnell, R., Williams, I., Von Oppell, U., & Wood, A. (2005). Giant aneurysms of the sinuses of  
56  
57 828 Valsalva and aortic regurgitation in a patient with Noonan's syndrome. *European Journal of*  
58  
59 829 *Cardio-Thoracic Surgery: Official Journal of the European Association for Cardio-Thoracic*  
60 830 *Surgery*, *28*(2), 346–348. <https://doi.org/10.1016/j.ejcts.2005.05.004>

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- 831 Rapezzi, C., Arbustini, E., Caforio, A. L. P., Charron, P., Gimeno-Blanes, J., Heliö, T., Linhart, A.,  
832 Mogensen, J., Pinto, Y., Ristic, A., Seggewiss, H., Sinagra, G., Tavazzi, L., & Elliott, P. M. (2013).  
833 Diagnostic work-up in cardiomyopathies: Bridging the gap between clinical phenotypes and final  
834 diagnosis. A position statement from the ESC Working Group on Myocardial and Pericardial  
835 Diseases. *European Heart Journal*, *34*(19), 1448–1458. <https://doi.org/10.1093/eurheartj/ehs397>
- 836 Rauen, K. A. (2013). The RASopathies. *Annual Review of Genomics and Human Genetics*, *14*,  
837 355–369. <https://doi.org/10.1146/annurev-genom-091212-153523>
- 838 Razzaque, M. A., Nishizawa, T., Komoike, Y., Yagi, H., Furutani, M., Amo, R., Kamisago, M.,  
839 Momma, K., Katayama, H., Nakagawa, M., Fujiwara, Y., Matsushima, M., Mizuno, K., Tokuyama,  
840 M., Hirota, H., Muneuchi, J., Higashinakagawa, T., & Matsuoka, R. (2007). Germline gain-of-  
841 function mutations in RAF1 cause Noonan syndrome. *Nature Genetics*, *39*(8), 1013–1017.  
842 <https://doi.org/10.1038/ng2078>
- 843 Roberts, A. E., Allanson, J. E., Tartaglia, M., & Gelb, B. D. (2013). Noonan syndrome. *Lancet*  
844 (*London, England*), *381*(9863), 333–342. [https://doi.org/10.1016/S0140-6736\(12\)61023-X](https://doi.org/10.1016/S0140-6736(12)61023-X)
- 845 Roberts, A. E., Araki, T., Swanson, K. D., Montgomery, K. T., Schiripo, T. A., Joshi, V. A., Li, L.,  
846 Yassin, Y., Tamburino, A. M., Neel, B. G., & Kucherlapati, R. S. (2007). Germline gain-of-  
847 function mutations in SOS1 cause Noonan syndrome. *Nature Genetics*, *39*(1), 70–74.  
848 <https://doi.org/10.1038/ng1926>
- 849 Rodriguez-Viciana, P., Tetsu, O., Tidyman, W. E., Estep, A. L., Conger, B. A., Cruz, M. S.,  
850 McCormick, F., & Rauen, K. A. (2006). Germline mutations in genes within the MAPK pathway  
851 cause cardio-facio-cutaneous syndrome. *Science (New York, N.Y.)*, *311*(5765), 1287–1290.  
852 <https://doi.org/10.1126/science.1124642>
- 853 Romano, A. A., Allanson, J. E., Dahlgren, J., Gelb, B. D., Hall, B., Pierpont, M. E., Roberts, A. E.,  
854 Robinson, W., Takemoto, C. M., & Noonan, J. A. (2010). Noonan syndrome: Clinical features,  
855 diagnosis, and management guidelines. *Pediatrics*, *126*(4), 746–759.  
856 <https://doi.org/10.1542/peds.2009-3207>
- 857 Ruiz-Llobet, A., Isola, I., Gassiot, S., Català, A., Díaz-Ricart, M., Martínez-Monseny, A. F.,  
858 Serrano, M., & Berrueco, R. (2020). Platelet Dysfunction in Noonan and 22q11.2 Deletion  
859 Syndromes in Childhood. *Thrombosis and haemostasis*, *120*(3), 457–465. [https://doi.org/10.1055/s-](https://doi.org/10.1055/s-0040-1701239)  
860 0040-1701239

- 1  
2  
3 861 Sarkozy, A., Conti, E., Seripa, D., Digilio, M. C., Grifone, N., Tandoi, C., Fazio, V. M., Di  
4 862 Ciommo, V., Marino, B., Pizzuti, A., & Dallapiccola, B. (2003). Correlation between PTPN11 gene  
5 863 mutations and congenital heart defects in Noonan and LEOPARD syndromes. *Journal of Medical*  
6 864 *Genetics*, 40(9), 704–708. <https://doi.org/10.1136/jmg.40.9.704>
- 7  
8 865 Sarkozy, A., Digilio, M. C., & Dallapiccola, B. (2008). Leopard syndrome. *Orphanet Journal of*  
9 866 *Rare Diseases*, 3, 13. <https://doi.org/10.1186/1750-1172-3-13>
- 10  
11 867 Scott, A., Giosaffatte, N. D., Pinna, V., Daniele, P., Corno, S., D'Ambrosio, V., Andreucci, E.,  
12 868 Marozza, A., Sirchia, F., Tortora, G., Mangiameli, D., Marco, C. D., Romagnoli, M., Donati, I.,  
13 869 Zonta, A., Grosso, E., Naretto, V. G., Mastromoro, G., Versacci, P., ... Luca, A. D. (2021). When  
14 870 to test fetuses for RASopathies? Proposition from a systematic analysis of 352 multicenter cases  
15 871 and a postnatal cohort. *Genetics in Medicine*, 23(6), 1116–1124. [https://doi.org/10.1038/s41436-](https://doi.org/10.1038/s41436-020-01093-7)  
16 872 [020-01093-7](https://doi.org/10.1038/s41436-020-01093-7)
- 17  
18 873 Shachter, N., Perloff, J. K., & Mulder, D. G. (1984). Aortic dissection in Noonan's syndrome (46  
19 874 XY turner). *The American Journal of Cardiology*, 54(3), 464–465. [https://doi.org/10.1016/0002-](https://doi.org/10.1016/0002-9149(84)90228-5)  
20 875 [9149\(84\)90228-5](https://doi.org/10.1016/0002-9149(84)90228-5)
- 21  
22 876 Shaw, A. C., Kalidas, K., Crosby, A. H., Jeffery, S., & Patton, M. A. (2007). The natural history of  
23 877 Noonan syndrome: A long-term follow-up study. *Archives of Disease in Childhood*, 92(2), 128–  
24 878 132. <https://doi.org/10.1136/adc.2006.104547>
- 25  
26 879 Smpokou, P., Tworog-Dube, E., Kucherlapati, R. S., & Roberts, A. E. (2012). Medical  
27 880 complications, clinical findings, and educational outcomes in adults with Noonan syndrome.  
28 881 *American Journal of Medical Genetics. Part A*, 158A(12), 3106–3111.  
29 882 <https://doi.org/10.1002/ajmg.a.35639>
- 30  
31 883 Stout, K. K., Daniels, C. J., Aboulhosn, J. A., Bozkurt, B., Broberg, C. S., Colman, J. M., Crumb, S.  
32 884 R., Dearani, J. A., Fuller, S., Gurvitz, M., Khairy, P., Landzberg, M. J., Saidi, A., Valente, A. M., &  
33 885 Van Hare, G. F. (2019). 2018 AHA/ACC Guideline for the Management of Adults With Congenital  
34 886 Heart Disease: A Report of the American College of Cardiology/American Heart Association Task  
35 887 Force on Clinical Practice Guidelines. *Circulation*, 139(14), e698–e800.  
36 888 <https://doi.org/10.1161/CIR.0000000000000603>
- 37  
38 889 Tartaglia, M., & Gelb, B. D. (2010). Disorders of dysregulated signal traffic through the RAS-  
39 890 MAPK pathway: Phenotypic spectrum and molecular mechanisms. *Annals of the New York*  
40 891 *Academy of Sciences*, 1214, 99–121. <https://doi.org/10.1111/j.1749-6632.2010.05790.x>

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50  
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54  
55  
56  
57  
58  
59  
60

- 892 Tartaglia, M., Kalidas, K., Shaw, A., Song, X., Musat, D. L., van der Burgt, I., Brunner, H. G.,  
893 Bertola, D. R., Crosby, A., Ion, A., Kucherlapati, R. S., Jeffery, S., Patton, M. A., & Gelb, B. D.  
894 (2002). PTPN11 Mutations in Noonan Syndrome: Molecular Spectrum, Genotype-Phenotype  
895 Correlation, and Phenotypic Heterogeneity. *The American Journal of Human Genetics*, *70*(6),  
896 1555–1563. <https://doi.org/10.1086/340847>
- 897 Tartaglia, M., Mehler, E. L., Goldberg, R., Zampino, G., Brunner, H. G., Kremer, H., van der Burgt,  
898 I., Crosby, A. H., Ion, A., Jeffery, S., Kalidas, K., Patton, M. A., Kucherlapati, R. S., & Gelb, B. D.  
899 (2001). Mutations in PTPN11, encoding the protein tyrosine phosphatase SHP-2, cause Noonan  
900 syndrome. *Nature Genetics*, *29*(4), 465–468. <https://doi.org/10.1038/ng772>
- 901 Tartaglia, M., Pennacchio, L. A., Zhao, C., Yadav, K. K., Fodale, V., Sarkozy, A., Pandit, B., Oishi,  
902 K., Martinelli, S., Schackwitz, W., Ustaszewska, A., Martin, J., Bristow, J., Carta, C., Lepri, F.,  
903 Neri, C., Vasta, I., Gibson, K., Curry, C. J., ... Gelb, B. D. (2007). Gain-of-function SOS1  
904 mutations cause a distinctive form of Noonan syndrome. *Nature Genetics*, *39*(1), 75–79.  
905 <https://doi.org/10.1038/ng1939>
- 906 Umeki, I., Niihori, T., Abe, T., Kanno, S., Okamoto, N., Mizuno, S., Kurosawa, K., Nagasaki, K.,  
907 Yoshida, M., Ohashi, H., Inoue, S., Matsubara, Y., Fujiwara, I., Kure, S., & Aoki, Y. (2019).  
908 Delineation of LZTR1 mutation-positive patients with Noonan syndrome and identification of  
909 LZTR1 binding to RAF1–PPP1CB complexes. *Human Genetics*, *138*(1), 21–35.  
910 <https://doi.org/10.1007/s00439-018-1951-7>
- 911 Wehrens, X. H., Lehnart, S. E., Reiken, S. R., Deng, S. X., Vest, J. A., Cervantes, D., Coromilas, J.,  
912 Landry, D. W., & Marks, A. R. (2004). Protection from cardiac arrhythmia through ryanodine  
913 receptor-stabilizing protein calstabin2. *Science (New York, N.Y.)*, *304*(5668), 292–296.  
914 <https://doi.org/10.1126/science.1094301>
- 915 Wolf, C. M., Zenker, M., Burkitt-Wright, E., Edouard, T., García-Miñaur, S., Lebl, J., Shaikh, G.,  
916 Tartaglia, M., Verloes, A., & Östman-Smith, I. (2022). Management of cardiac aspects in children  
917 with Noonan syndrome—Results from a European clinical practice survey among paediatric  
918 cardiologists. *European Journal of Medical Genetics*, *65*(1), 104372.  
919 <https://doi.org/10.1016/j.ejmg.2021.104372>
- 920 Yamamoto, G. L., Agüena, M., Gos, M., Hung, C., Pilch, J., Fahiminiya, S., Abramowicz, A.,  
921 Cristian, I., Buscarilli, M., Naslavsky, M. S., Malaquias, A. C., Zatz, M., Bodamer, O., Majewski,  
922 J., Jorge, A. A. L., Pereira, A. C., Kim, C. A., Passos-Bueno, M. R., & Bertola, D. R. (2015). Rare

1  
2  
3 923 variants in *SOS2* and *LZTR1* are associated with Noonan syndrome. *Journal of Medical Genetics*,  
4 924 52(6), 413–421. <https://doi.org/10.1136/jmedgenet-2015-103018>  
5  
6  
7 925 Yaoita, M., Niihori, T., Mizuno, S., Okamoto, N., Hayashi, S., Watanabe, A., Yokozawa, M.,  
8 926 Suzumura, H., Nakahara, A., Nakano, Y., Hokosaki, T., Ohmori, A., Sawada, H., Migita, O., Mima,  
9 927 A., Lapunzina, P., Santos-Simarro, F., García-Miñaur, S., Ogata, T., ... Aoki, Y. (2016). Spectrum  
10 928 of mutations and genotype–phenotype analysis in Noonan syndrome patients with RIT1 mutations.  
11 929 *Human Genetics*, 135(2), 209–222. <https://doi.org/10.1007/s00439-015-1627-5>  
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## 19 931 **FIGURE LEGENDS**

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21 932 **Figure 1.** Diagnosis–treatment flow-chart for congenital heart defects associated with  
22 933 RASopathies.

24 934 Abbreviations: CHDs, congenital heart defects; PVS, pulmonary valve stenosis; ASD, atrial  
25 935 septal defect; AVSD, atrioventricular septal defect; VSD, ventricular septal defect; PDA, patent  
26 936 ductus arteriosus; MV, mitral valve; ECG, electrocardiogram.

29 937 **Figure 2.** Diagnostic flow-chart for hypertrophic cardiomyopathy associated with  
30 938 RASopathies.

32 939 Abbreviations: ASD, atrial septal defect; AVSD, atrioventricular septal defect; CHDs,  
33 940 congenital heart defects; CS, Costello syndrome; MV, mitral valve; NGS, next-generation  
34 941 sequencing; NSML, Noonan syndrome with multiple lentigines; PVS, pulmonary valve stenosis;  
35 942 VSD, ventricular septal defect.

38 943 **Figure 3.** Determinants and management of left ventricular outflow tract obstruction in  
39 944 hypertrophic cardiomyopathy associated with RASopathies.  
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## THE HEART IN RASOPATHIES

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## ABSTRACT

The cardiovascular phenotype associated with RASopathies has expanded far beyond the original descriptions of pulmonary valve stenosis by Dr. Jaqueline Noonan in 1968 and hypertrophic cardiomyopathy by Hirsch *et al* in 1975. Because of the common underlying RAS/MAPK pathway dysregulation, RASopathy syndromes usually present with a typical spectrum of overlapping cardiovascular anomalies, although less common cardiac defects can occur. ~~Because of the common underlying RAS/MAPK pathway dysregulation, RASopathy syndromes have overlapping cardiac features and usually present with a typical spectrum of cardiovascular anomalies, although less common cardiac defects can occur.~~ The identification of the causative genetic variants has enabled the recognition of specific correlations between genotype and cardiac phenotype. Characterization~~Determination~~ and understanding of genotype–phenotype associations is not only important for counselling a family of an infant with a new diagnosis of a RASopathy condition but is also critical for their clinical prognosis with respect to cardiac disease, neurodevelopment and other organ system involvement over the lifetime of the patient. This review will focus on the cardiac manifestations of the most common RASopathy syndromes, the relationship between cardiac defects and causal genetic variation, the contribution of cardiovascular abnormalities to morbidity and mortality and the most relevant follow-up issues for patients affected by RAS/MAPK pathway diseases, with respect to cardiac clinical outcomes and management, in children and in the adult population.

## KEYWORDS

RASopathy, Congenital heart disease, Hypertrophic cardiomyopathy, Noonan syndrome, Cardio-facio-cutaneous syndrome, Costello syndrome, Noonan syndrome with multiple lentigines.

## INTRODUCTION

Congenital heart defects (CHDs) and hypertrophic cardiomyopathy (HCM) are common features in RASopathies, with a prevalence from 60 to 90% in affected patients, as previously reported by several studies (Calcagni et al., 2020; Jhang et al., 2016; Lin et al., 2011; Linglart & Gelb, 2020; Prendiville et al., 2014).

As for other genetic syndromes, the presence of a cardiac disease can be the clinical finding that leads to the diagnosis, and RASopathies should always be considered in the differential diagnosis of children with HCM, in particular when other systemic or cardiac features of these traits are present (*e.g.*, short stature, hypertelorism, cryptorchidism, pulmonary valve stenosis) (Limongelli et al., 2020).

The prenatal recognition of some cardiac defects (*e.g.*, pulmonary valve stenosis and/or HCM), especially when associated with certain specific ultrasound findings, such as increased nuchal translucency or nuchal fold, polyhydramnios, cystic hygroma, hydrops fetalis, ascites/thoracic effusion or lymphatic dysplasia, can help to guide the differential diagnosis of RASopathies and define the indication for molecular genetic testing (Digilio et al., 2011; Myers et al., 2014; Scott et al., 2021).

~~As a rule of thumb~~In general, all patients should undergo a thorough cardiac assessment after the diagnosis, including ECG and two-dimensional color Doppler echocardiography, followed by regular cardiac surveillance based on the cardiac phenotype and on the specific genetic cause (Linglart & Gelb, 2020).

This review will focus on: (a) the cardiac manifestations of the most common RASopathy syndromes, (b) the relationship between cardiac defects and causal genetic variation, (c) the contribution of cardiovascular abnormalities to morbidity and mortality and (d) the most relevant follow-up issues for patients affected by RAS/MAPK pathway diseases, with respect to cardiac clinical outcomes and management, in children and in the adult population.

## 1. CONGENITAL HEART DEFECTS IN RASOPATHIES

### 1.1 Cardiovascular anomalies and genotype-phenotype correlation

RASopathy syndromes are a heterogeneous group of genetic multisystemic disorders caused by germline mutations in genes that encode proteins of the RAS/MAPK signal transduction pathway. Because of the common underlying RAS/MAPK pathway dysregulation, these syndromes have overlapping cardiac features and usually present with a typical spectrum of CHDs (Aoki et al., 2016; Rauen, 2013; Tartaglia & Gelb, 2010).

Among RASopathies, the most common syndromes are Noonan syndrome (~~NS~~, OMIM PS163950), cardio-facio-cutaneous syndrome (CFCS, OMIM #115150), Costello syndrome (~~CS~~, OMIM #218040), and Noonan syndrome with multiple lentigines (NSML, OMIM #151100).

The most common CHDs shown to be associated with these RASopathies include pulmonary valve stenosis (PVS), atrioventricular septal defect (AVSD) and atrial septal defect (ASD) (Calcagni et al., 2017; Digilio et al., 2013; Linglart & Gelb, 2020).

PVS represents the most recurrent CHD, reported in about 50% of individuals affected by Noonan syndrome (Bell et al., 2021; Roberts et al., 2013). The stenotic PV often has typical anatomic features, showing a dysplastic phenotype with myxomatous thickening and poorly mobile leaflets, resulting in severe right ventricular outflow tract obstruction. In some cases, PVS is supra-annular, with fusion of valvular cusps with the wall of the pulmonary artery (Digilio et al., 2009). In this regard, a thorough echocardiographic assessment of the site of obstruction and valvular morphology is fundamental to choose the optimal type of repair between balloon valvuloplasty and surgical treatment (Lin et al., 2008; McCrindle, 1994; Prendiville et al., 2014).

The reported prevalence of PVS in CFCS is ranging from 31% to 44% based on different cohorts (Allanson et al., 2011; Lin et al., 2011; Pierpont et al., 2014; Rodriguez-Viciano et al., 2006). In Costello syndrome, PVS is present in 15-20% of cases, associated with sub-valvular and supra-valvular pulmonary stenosis. PVS may frequently be the result of sub-pulmonary muscular obstruction related to HCM. Rarely, severe forms of sub-valvular pulmonary stenosis have been described as “double-chambered right ventricle” (Gripp et al., 2019; Lin et al., 2011). Compared to other RASopathies, patients with Costello syndrome are less likely to have a severe form of PVS (Lin et al., 2011). Similarly, PVS in NSML is rare, mostly associated with HCM (Sarkozy et al., 2008).

AVSD represents a relatively common feature in Noonan syndrome ~~NS~~ with prevalence of about 15% (Linglart & Gelb, 2020; Marino et al., 1999), most frequently reported as partial AVSD

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3 130 and more rarely as complete AVSD (Digilio et al., 2013; Pradhan et al., 2013). AVSD in Noonan  
4 syndromeNS may be associated with other cardiac defects including subaortic stenosis, structural  
5 131 mitral valve (MV) anomalies, PVS and HCM (Digilio et al., 2013; Marino et al., 1995, 1999;  
6 132 Pradhan et al., 2013).  
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8 133

9  
10 134 In patients with Noonan syndromeNS, left-sided obstructive cardiac lesions have also been  
11 reported in the absence of HCM spectrum. In particular, anatomic obstructions have been described  
12 135 at valvular or sub-valvular level (Burch et al., 1993), in subaortic location, as a result of left  
13 136 ventricular valve anomalies (Marino et al., 1995) or as coarctation of the aorta (CoA) (Digilio et al.,  
14 137 1997, 1998). Data on the prevalence of left-sided obstructions in Noonan syndromeNS vary widely  
15 138 in the different reported cohorts, ranging from 2% to 12.5% for CoA and 2% to 17% for left-sided  
16 139 valve abnormalities (Colquitt & Noonan, 2014; Digilio et al., 1998; Digilio & Marino, 2001;  
17 140 Prendiville et al., 2014).  
18  
19 141

20 142 In addition, atypical ~~cardiac-defects~~CHD-(ACDs) have been described, also as isolated  
21 143 cardiovascular lesions (Calcagni et al., 2020; Leoni et al., 2022; Linglart & Gelb, 2020), including  
22 144 mitral and aortic valve dysfunction, abnormalities of ascending and descending aorta, coronary  
23 145 artery ~~(CA)~~dilation, enlargement of the left atrial appendage and isolated pulmonary branches  
24 146 diseases. MV abnormalities most frequently occur as a minor valvular dysfunction without clinical  
25 147 relevance, due to redundant MV leaflets and/or elongated chords (Leoni et al., 2022). However,  
26 148 moderate-to-severe regurgitation can also occur, in case of dysplastic leaflets and/or significant MV  
27 149 prolapse (Calcagni et al., 2020; Linglart & Gelb, 2020). Since MV abnormalities might present as  
28 150 isolated valve disorder, specifically without concomitant HCM, this raises the concern that  
29 151 RAS/MAPK pathway dysregulation may independently affect the morphogenesis of the MV  
30 152 apparatus.  
31  
32

33 153 Since 2001 when *PTPN11* gene missense mutations were found to be causative of Noonan  
34 154 syndromeNS (Tartaglia et al., 2001), several studies have described the association between  
35 155 mutations in genes encoding components of the RAS/MAPK signalling pathway and RASopathies  
36 156 (Aoki et al., 2016). Congenital heart anomalies occur with different frequency among RASopathy  
37 157 syndromes as a result of mutations in different genes, making it possible to delineate specific  
38 158 correlations between genotype and cardiac phenotype.  
39  
40

41 159 PVS is the most frequent cardiovascularae defectisease in patients with Noonan  
42 160 syndromeNS due to variants of *PTPN11*, with an approximate prevalence of 70% (Calcagni et al.,  
43 161 2017; Digilio et al., 2010; Prendiville et al., 2014); specifically, an association between PVS and  
44 162 mutation on codon 308 of the gene has been recognized (Sarkozy et al., 2003; Tartaglia et al.,  
45 163 2002). In these patients, a high prevalence of a severe form of pulmonary stenosis, both at valvular

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3 164 and supravulvar levels and in association with dysplastic PV, has been described (Leoni et al.,  
4 165 2022). Atrial septal defect (ASD), isolated or in association with PVS, is commonly detected in  
5 166 individuals with Noonan syndrome~~NS~~-*PTPN11* abnormalities, with a specific correlation of  
6 167 mutations on exon 3 of the gene (Sarkozy et al., 2003). Hemodynamically significant MV  
7 168 anomalies and AVSD can also be observed in patients with *PTPN11* variants, whereas tetralogy of  
8 169 Fallot, ventricular septal defect, patent ductus arteriosus and left-sided obstructions are less  
9 170 frequently reported (Digilio et al., 2013; Leoni et al., 2022; Marino et al., 1995; Prendiville et al.,  
10 171 2014). Conversely, *PTPN11* mutations on exon 7, 12 and 13 are associated with a small subset of  
11 172 CHDs in patients with NSML (Kauffman et al., 2021; Sarkozy et al., 2003). *PTPN11* is the most  
12 173 commonly mutated gene in patients with RASopathies and atypical CHD-ACDs, such as aortic  
13 174 insufficiency, coronary artery CA-dilation (particularly in patients with NSML), left atrial  
14 175 appendage dilatation and isolated pulmonary arteries anomalies (Calcagni et al., 2020).

15 176 Among patients with *SOS1* variants, PVS of mild degree, often associated with ASD, is the  
16 177 most commonly described cardiac abnormality, followed by different types of valve diseases (Leoni  
17 178 et al., 2022; Roberts et al., 2007; Tartaglia et al., 2007). The cardiac phenotype associated with  
18 179 *SOS2* pathogenic variants is similar to the one described in association with *SOS1*, with pulmonary  
19 180 stenosis and septal defects being the most recurrent diseases (Cordeddu et al., 2015; Yamamoto et  
20 181 al., 2015). In individuals harboring pathogenic variants in *KRAS*, the heart is involved in the  
21 182 majority of cases without correlation with a specific cardiac phenotype, even though PVS seems to  
22 183 have a slightly greater prevalence over the other cardiac defects (Leoni et al., 2022; Pierpont &  
23 184 Digilio, 2018). In the subgroup of subjects with causal variation in *RAF1*, CHDs are poorly  
24 185 represented, with PVS and ASD being the most common defects (Kobayashi et al., 2010; Pandit et  
25 186 al., 2007; Razzaque et al., 2007). The prevalence of cardiovascular involvement in individuals  
26 187 harboring *RIT1* alleles ranges between 90 and 100%, with a strong correlation with PVS (Aoki et  
27 188 al., 2013; Yaoita et al., 2016). *LZTR1* cardiac phenotype includes different types of CHDs, most  
28 189 often ASD and PVS (Chinton et al., 2020; Umeki et al., 2019; Yamamoto et al., 2015).

29 190 Noonan syndrome with loose anagen hair (NSLAH) due to *SHOC2* gene variants seems to  
30 191 have correlation with PVS, MV dysplasia and septal defects (Cordeddu et al., 2009; Komatsuzaki et  
31 192 al., 2010). Less than half of patients with *HRAS* pathogenic variants, which underlie Costello  
32 193 syndrome~~CS~~, shows CHDs, particularly PVS and MV anomalies, mostly in association with HCM  
33 194 (Lin et al., 2011). Finally, the most frequent CHD in CFCS caused by *BRAF*, *MAP2K1* and  
34 195 *MAP2K2* variants is PVS, followed by ASD (Allanson et al., 2011; Armour & Allanson, 2007;  
35 196 Yaoita et al., 2016).

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3 197 Although many correlations between genetic variants and CHDs have been established,  
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5 198 others may not have emerged due to the small patient numbers, indicating that further research is  
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7 199 needed.

### 8 200 9 10 201 *1.2 Management options and outcome*

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12 202  
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14 203 The management of CHDs in RASopathies depends on the nature of the specific heart defect  
15 204 (**Figure 1**). However, when considering cardiac outcomes and necessities during the follow-up  
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17 205 period, cardiac defects can vary in terms of spectrum and severity, and consequently, their clinical  
18  
19 206 involvement is quite heterogeneous.

20  
21 207 In **Noonan syndromeNS**, PVS shows differing degrees of severity: mild in ~60% of patients,  
22 208 moderate in ~10% and severe in ~30% (Colquitt & Noonan, 2014; Shaw et al., 2007). Usually, the  
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24 209 mild form of PVS is nonprogressive and is unlikely to require intervention (Colquitt & Noonan,  
25  
26 210 2014). Conversely, moderate-to-severe stenosis carries a higher rate of intervention, as a  
27  
28 211 consequence of a higher degree of dysplasia of the valve leaflets. Patients with severe PVS very  
29 212 often undergo therapeutic procedure, often within two years of the diagnosis. Due to the distinct  
30  
31 213 anatomic features of the pulmonary valve, the standard approach using percutaneous balloon  
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33 214 valvuloplasty has been showed to be rarely successful in these patients (Linglart & Gelb, 2020),  
34  
35 215 who need to undergo percutaneous re-intervention or surgical treatment (either valvotomy or valve  
36 216 leaflet excisions) (Hemmati et al., 2019; Lin et al., 2008; McCrindle, 1994; Prendiville et al., 2014).  
37  
38 217 In 2018, Holzmann and colleagues reported their results concerning the immediate response to  
39 218 primary balloon pulmonary valvuloplasty. These results appeared sub-optimal in terms of reduction  
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41 219 of right ventricle-pulmonary artery gradient with a higher reintervention rate when compared to  
42  
43 220 non-syndromic patients (Holzmann et al., 2018). Therefore, with regard to risk of re-operation, a  
44  
45 221 second procedure is frequently required, mostly due to the reoccurrence of PVS (Burch et al., 1993;  
46 222 Calcagni et al., 2017). Except for severe forms of PVS or PVS associated with other CHDs, the  
47  
48 223 limited data available in literature on cardiac surgical prognosis in **Noonan syndromeNS** report that  
49  
50 224 the early postoperative outcomes for these patients with PVS are comparable to those of non-  
51  
52 225 syndromic patients (Hemmati et al., 2019).

53 226 Patients with AVSD frequently require an earlier intervention compared to individuals with  
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55 227 **Noonan syndromeNS** affected by other cardiac anomalies (Calcagni et al., 2017). The concurrence  
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57 228 of MV and/or aortic valve abnormalities in patients with AVSD results in a more complex and  
58  
59 229 severe cardiac phenotype, deserving a careful evaluation for a more appropriate surgical approach  
60 230 (Calcagni et al., 2017).



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3 231 Left-sided obstructive cardiac lesions usually require surgical treatment. Indications for  
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5 232 intervention and surgical results vary widely and depend on the severity of the stenosis, the  
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7 233 presence of multilevel left heart obstruction, other associated cardiac lesions or other non-cardiac  
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9 234 risk factors. There is evidence that structural abnormalities of the MV may not only contribute to  
10 235 the development of a subaortic gradient in patients with obstructive HCM and mild septal  
11  
12 236 hypertrophy but might also affect the surgical outcome in patients with CHDs (Calcagni et al.,  
13  
14 237 2017). Another risk factor for morbidity and mortality is the occurrence of subaortic stenosis,  
15 238 probably due to the presence of accessory fibrous connective tissue and/or anomalous MV insertion  
16  
17 239 or abnormality of the left ventricular papillary muscles (Digilio et al., 1998; Marino et al., 1995).

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19 240 Among atypical CHDAEDs, increased awareness of the significance of MV anomalies has  
20  
21 241 ensured that MV morphology and function are carefully investigated for their possible clinical  
22 242 relevance, allowing an early detection of valvular dysfunction. Interestingly, recent studies  
23  
24 243 highlighted the concomitance of congenital dysplasia of two or more cardiac valves, described as  
25  
26 244 “congenital polyvalvular disease”, suggesting a new distinct cardiovascular phenotype of the  
27 245 RASopathies, with implications for diagnosis and management (Leoni et al., 2022; Matalon et al.,  
28  
29 246 2021). All these data raise the concern that also atypical CHDAEDs need to be carefully  
30  
31 247 investigated and continuously monitored for their possible impact on the clinical outcome (Calcagni  
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33 248 et al., 2020; Romano et al., 2010; Wolf et al., 2022). Most frequently, cardiac surgery is not  
34 249 required, as minor CHDs have often a favorable outcome (Calcagni et al., 2020). However, when a  
35  
36 250 minor lesion is associated to major cardiac defects, the latter will direct the need for intervention  
37  
38 251 and the short-term and long-term outcomes.

39 252 Overall mortality in patients with RASopathies is low, being less than 2.5% in the overall  
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41 253 population and less than 3% in the subgroup with cardiac disease, with flat survival curves  
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43 254 (Calcagni et al., 2017). Linglart and Gelb found a similar length of hospital stay comparing patients  
44  
45 255 with and without an associated syndrome (Linglart & Gelb, 2020). With respect to mortality, the  
46 256 adverse event generally occurs in the first two years of life, or during the adulthood. Overall  
47  
48 257 mortality in the atypical CHDAEDs subgroup is reduced when compared to typical cardiac  
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50 258 diseases.

51 259 For adults with RASopathies, clear evidence is still lacking in the current literature.  
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53 260 Nonetheless, a previous study by Pierpont and Digilio highly recommended close follow-up for  
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55 261 such patients (Pierpont & Digilio, 2018). In their adult cohort, almost one-half needed cardiac  
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57 262 surgery and almost 3.5% experienced an arrhythmic event. In patients with PVS, long term sequelae  
58 263 of chronic pulmonary regurgitation might be expected after surgical or catheter intervention. Even  
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60 264 in the absence of specific data in literature, the management of these patients should be similar to

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3 255 non-syndromic ones, needing pulmonary reevaluation later in life, when patients become  
4 256 symptomatic or when progressive RV dilatation or dysfunction occurs (Baumgartner et al., 2021;  
5 257 Stout et al., 2019). Although cardiac complications are common findings in the adult population,  
6 258 these heart diseases are usually stable and non-progressive after the surgical procedure (Smpokou et  
7 259 al., 2012).

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10 270 Some adults with RASopathies were rarely found to have cardiac abnormalities other than  
11 271 structural CHDs, such as aortic root aneurysm, dilation of the ascending aorta, aortic dissection and  
12 272 giant aneurysms of the sinuses of Valsalva, in particular in Noonan syndrome patients with  
13 273 *PTPN11* mutations (Morgan et al., 1989; Power et al., 2006; Purnell et al., 2005; Shachter et al.,  
14 274 1984). In a retrospective study, Cornwall et al reported that aortic root aneurysms (defined as z-  
15 275 score  $\geq 2$ ) were prevalent in Noonan syndrome patients (~20%), often presenting during  
16 276 childhood, detected by routine screening and progressing over time (Cornwall et al., 2014). These  
17 277 findings imply that some individuals with Noonan syndrome may have connective tissue disorder-  
18 278 like vascular changes in adulthood, suggesting that all adults with Noonan syndrome should have  
19 279 lifelong cardiac follow-up.

20 280 Coronary artery CA-dilation, either isolated or with HCM, has also been reported in patients  
21 281 with RASopathies (Calcagni et al., 2016, 2020; Pacileo et al., 2006). In the setting of HCM,  
22 282 coronary artery CA-ectasia likely reflects the consequences of increased myocardial mass, left  
23 283 ventricle outflow tract obstruction and diastolic dysfunction (Limongelli et al., 2007). Conversely,  
24 284 in patients without HCM or any other coexistent cardiovascular defects, CAcoronary artery-ectasia  
25 285 ectasia could be related to the RAS-MAPK system dysregulation itself (Calcagni et al., 2020).  
26 286 Although the clinical significance and long-term outcome of this finding remain to be clarified,  
27 287 clinicians should be aware of the increased cardiovascular risk in these patients, and careful  
28 288 coronary multimodality imaging, including coronary CT angiography or MRI angiography, is  
29 289 mandatory to monitor whether this anomaly may progress. Especially in adulthood, it is essential to  
30 290 prevent risk factors for myocardial infarction, such as systemic hypertension and  
31 291 hypercholesterolemia, which could accelerate atherosclerotic coronary arteryCA disease. In such  
32 292 cases, use of antiplatelet or anticoagulant to prevent coronary artery CA-thrombosis might be  
33 293 considered.

34 294 Of note, non-cardiac comorbidities may influence the cardiac surgery outcome, such as  
35 295 lymphatic abnormalities resulting in chylothorax in up to 10% (Hemmati et al., 2019) and bleeding  
36 296 diathesis, widely ranging in prevalence from 50% to 89% when considering either a history of  
37 297 bleeding and/or abnormal hemostatic lab results (Briggs & Dickerman, 2012; Artoni et al., 2014).  
38 298 Indeed, a wide spectrum of bleeding abnormalities including coagulation factor deficiency and

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3 299 platelet dysfunction has been described in patients with RASopathies, leading to possible bleeding  
4 300 complications during and after surgical procedures (Di Candia et al., 2021; Ruiz-Llobet et al.,  
5 301 2020). Thus, it is essential to investigate the coagulation system in these patients.  
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## 10 303 11 12 304 **2. HYPERTROPHIC CARDIOMYOPATHY IN RASOPATHIES**

### 13 14 305 15 306 *2.1 Cardiovascular anomalies and genotype-phenotype correlation*

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19 308 In recent longitudinal cohorts of pediatric patients with HCM, RASopathies represent a  
20 309 common underlying etiology (approx. 20% of cases), with the highest prevalence of HCM in  
21 310 infancy (up to 42% of cases) (Alexander et al., 2018; Norrish et al., 2019) and a significant  
22 311 morbidity and mortality among affected individuals (Lioncino et al., 2022).  
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26 312 The occurrence of HCM is heterogeneous among the different RASopathies. The prevalence  
27 313 is highest in NSML, where HCM is diagnosed in up to 80% of patients, generally occurring during  
28 314 infancy (Limongelli et al., 2007). On the other hand, it occurs less frequently in the other  
29 315 RASopathies: 65% in [Costello syndromeCS](#), 40% in CFCS, 20-25% in [Noonan syndromeNS](#)  
30 316 (Monda, Rubino, et al., 2021).  
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34 317 It has been suggested that the pathophysiology of HCM is related to a hyperactivation of the  
35 318 RAS-MAPK cascade, responsible for cardiomyocyte hypertrophy and myocardial disarray.  
36 319 However, this pathophysiological mechanism cannot be generalized to all RASopathies. For  
37 320 example, variants in *PTPN11* associated with [Noonan syndromeNS](#) are different from those related  
38 321 to NSML (Gelb & Tartaglia, 2011). While [Noonan syndromeNS](#)-related variants behave as a gain-  
39 322 of-function alleles with increased basal phosphatase activity (Keilhack et al., 2005), NSML-related  
40 323 variants are responsible for catalytic impairment (Lauriol & Kontaridis, 2011). Thus, in *PTPN11*  
41 324 [Noonan syndromeNS](#)-related variants the mechanism of HCM development is the upregulation of  
42 325 MAPK signaling, while *PTPN11* hypomorphic mutants associated with NSML cause enhanced  
43 326 signal flow through the PI3K-AKT-mTOR pathway. The elucidation of the pathophysiology of  
44 327 RASopathy-related HCM has significant clinical relevance for the possible development of targeted  
45 328 therapies.  
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### 55 329 56 57 330 *2.2 Clinical features and diagnosis*

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3 332 HCM in RASopathies has higher risk of death and transplantation when compared to non-  
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5 333 syndromic forms. When presenting below the 6 months of age with symptoms of heart failure, there  
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7 334 is a higher risk of mortality, reaching early 22% at 1 year (6-fold higher than non-syndromic  
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9 335 forms). While in surviving subjects without symptoms of heart failure, sudden cardiac death (SCD)  
10 336 is more frequent among adolescents and young adults (Alexander et al., 2018).

11  
12 337 HCM in RASopathies is characterized by a more severe left ventricular hypertrophy (LVH)  
13  
14 338 and a higher prevalence and severity of left ventricular outflow tract obstruction (LVOTO)  
15 339 compared with non-syndromic forms (Cerrato et al., 2008). Several factors contribute to generating  
16  
17 340 LVOTO, including systolic anterior motion (SAM) of the MV, the displacement of papillary  
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19 341 muscles, the anomalous insertion of mitral chordae, and an accessory fibrous connective tissue that  
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21 342 can cause subaortic stenosis. These complex mechanisms for LVOTO result in a high risk for  
22 343 reintervention and death (Calcagni et al., 2017). Biventricular hypertrophy, due to the coexistence  
23  
24 344 of HCM and PVS, is relatively common and may represent a specific red flag for RASopathies  
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26 345 (Limongelli et al., 2020). Coronary artery CA abnormalities are commonly identified (up to 30%)  
27 346 and contribute to myocardial ischemia, worsening the imbalance between myocardial oxygen  
28  
29 347 supply and demand (Calcagni et al., 2020). In less than 6% of cases, MV abnormalities cause severe  
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31 348 mitral regurgitation, making more prone to symptoms for heart failure (Marino et al., 1995).  
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33 349 Decreased height-for-age and lower left ventricular fractional shortening z-score are independent  
34 350 predictors of mortality in patients with Noonan syndromeNS with HCM.

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36 351 Several ECG abnormalities have been reported, with signs of LVH and diffuse  
37  
38 352 repolarization abnormalities representing the most common findings. In addition, extreme right axis  
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40 353 deviation (a “superior” QRS axis) represents a specific disease marker, commonly identified in  
41 354 patients with Noonan syndromeNS with biventricular hypertrophy (Limongelli et al., 2020; Rapezzi  
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43 355 et al., 2013). Other ECG abnormalities that could be encountered are pseudo-infarction q waves and  
44  
45 356 prolonged QT interval (Limongelli et al., 2008). Atrial tachyarrhythmias are commonly experienced  
46 357 by patients with Costello syndromeCS (in more than 50%), but the natural history is usually benign,  
47  
48 358 with a high rate of responsiveness to medical therapy and spontaneous regression within the first  
49  
50 359 year of life (Levin et al., 2018). However, atrial tachycardia is not an exclusive feature of the  
51  
52 360 Costello Syndrome (Lin et al., 2011). Non-reentrant atrial tachycardias (such as multifocal atrial  
53 361 tachycardia and ectopic atrial tachycardia) have also been reported in patients with Noonan  
54  
55 362 syndrome (with RAF1, SOS1 and PTPN11 mutated genes). Furthermore, patients with mutation of  
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57 363 PTPN11 gene in the spectrum of NSML may present with atrial disorders (Levin et al., 2018). Even  
58 364 rare, these atrial arrhythmias may appear in early infancy or in the first 1-2 months of life. These  
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forms present with a high ventricular rate and are often a challenge to be controlled by the medical treatment.

Atrial tachycardia in RASopathy patients may occur in the presence or absence of HCM. In addition, these atrial arrhythmias could cause tachycardia-induced cardiomyopathy with a reduced cardiac function or they may be a consequence of cardiomyopathy itself. Patients without HCM frequently experience a hyperdynamic left ventricle which probably may be related to the increased intracellular calcium. Disorders of intracellular calcium homeostasis have also been reported in RASopathies and may influence the management of antiarrhythmic therapy (Wehrens et al., 2004).

A recent study investigated the morphology of the ventricular septum determined by echocardiography, comparing patients with NSML and Noonan syndrome NS-patients. In this study, a sigmoid septum and a ventricular septal bulge were observed predominantly in NSML patients, whereas biconvex septa were more common in Noonan syndrome NS patients. Furthermore, each cardiac phenotype showed association with specific genotypes and the clearest genotype-cardiac phenotype association occurred in patients carrying variants affecting specific exons of *PTPN11* (Kauffman et al., 2021). A more recent study confirmed the sigmoid-shaped ventricular septum morphology in a small subset of patients of its cohort of 116 cases, occurring in different RASopathies and associated with pathogenic variants involving multiple genes (Delogu et al., 2022). Whether ventricular septum morphology represents a distinct cardiac phenotype in RASopathies with correlations between echocardiographic features and the involved gene/variant remains to be addressed with further research.

The diagnostic algorithm for the diagnosis of HCM-related RASopathy is described in **Figure 2**. In summary, in patients fulfilling the diagnostic criteria for HCM (maximal left ventricular wall thickness  $\geq 15$  mm or  $\geq 13$  mm, without or with family history for HCM in adults, respectively, or  $\geq 2$  z-score in children), attention should be paid to identifying diagnostic clues suggestive for RASopathies (Authors/Task Force members et al., 2014; Limongelli et al., 2022; Ommen et al., 2020). In these patients, genetic testing for the identification of the disease-causing mutation is required for the diagnosis.

### 2.3 Management options and outcomes

The diagnosis of HCM represents a major prognostic determinant in patients with RASopathies since the severity of the cardiac phenotype is associated with a low survival rate and high risk of death (Calcagni et al., 2017).

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3 398 The risk for SCD appears to be significantly lower compared with patients with sarcomeric  
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5 399 variants, but risk stratification for SCD in patients with RASopathies is challenging (Monda,  
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7 400 Lioncino, Rubino, et al., 2022). In non-syndromic HCM, a previous history of sudden cardiac  
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9 401 arrest, sustained or non-sustained ventricular tachycardia, unexplained syncope, and massive LVH  
10 402 have been suggested as risk factors for SCD, and in their presence, implantable cardioverter  
11  
12 403 defibrillation (ICD) implantation may be considered (Monda, Lioncino, Rubino, et al., 2022;  
13  
14 404 Ommen et al., 2020). The relevance of these clinical features in RASopathy patients need to be  
15 405 confirmed.  
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17 406 Medical therapy in patients with RASopathy-related HCM is mainly focused on managing  
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19 407 symptoms associated with LVOTO (Limongelli et al., 2022) (**Figure 3**). Non-vasodilating beta-  
20  
21 408 blockers represent the first line and should be titrated to the maximum tolerated dose to obtain a  
22 409 LVOT gradient target <50 mmHg (i.e., the threshold for invasive strategy) (Authors/Task Force  
23  
24 410 members et al., 2014; Monda, Lioncino, Palmiero, et al., 2022; Ommen et al., 2020). Non-  
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26 411 vasodilating calcium antagonists should be considered when beta-blockers are contraindicated or  
27  
28 412 not tolerated. However, their use should be carefully monitored since a rare association with severe  
29 413 bradycardia or heart failure worsening in infants treated with verapamil has been reported (Moran  
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31 414 & Colan, 1998). Disopyramide may be considered in addition to beta-blockers to reduce the degree  
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33 415 of obstruction and improve symptoms. This drug has proved to be effective also in [Noonan](#)  
34 416 [syndrome](#)<sup>NS</sup>, but the magnitude of reduction should be tempered because the effect is temporary  
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36 417 (O'Connor et al., 2018). Surgical myectomy is the treatment of choice for patients with LVOTO  
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38 418 who remain symptomatic despite optimal medical therapy. Patients with biventricular obstruction  
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40 419 with severe PVS usually manifest severe heart failure and symptoms refractory to medical therapy.  
41 420 Pulmonary valvuloplasty is often ineffective in patients with RASopathies, and surgical repair is  
42  
43 421 generally required.  
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45 422 Orthotopic heart transplantation is rarely required in patients with RASopathies. It should be  
46 423 considered in patients with severe heart failure and refractoriness to medical therapy, intractable  
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48 424 ventricular arrhythmias, cardiogenic shock requiring inotropes, severe diastolic dysfunction or in  
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50 425 patients with severe LVOTO when surgical myectomy is not effective or feasible (Limongelli et al.,  
51  
52 426 2022; Monda, Lioncino, et al., 2021). The evaluation for indication to transplant should assess the  
53 427 cardiac and non-cardiac risk (Gajarski et al., 2009). Knowledge of specific mutation should be of  
54  
55 428 particular value in risk assessment: *PTPN11 p.Gln510Glu* mutation should be considered for an  
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57 429 earlier evaluation for transplant. Also, *PTPN11*- and *RIT1*-associated [Noonan syndrome](#)<sup>NS</sup>-patients  
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59 430 have a known coagulopathy risk. Other mutations carry a higher risk for malignancies. This  
60 431 information should be taken into account when assessing the individual risk prior to transplant

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3 432 listing. Growth issues and gastrostomy feeding are also commonly encountered in post-transplant  
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5 433 management (McCallen et al., 2019). Treatment of RASopathies with therapies targeting the  
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7 434 RAS/MAPK cascade (in Noonan syndrome) or the PI3K/AKT/mTor pathway (in NSML) are  
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9 435 limited to case reports suggesting a beneficial effect of these therapeutic approaches in improving  
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11 436 clinical status and resulting in LVH regression (Andelfinger et al., 2019; Marin et al., 2011; Nakano  
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13 437 et al., 2022; Mussa et al., 2021). MEK inhibition, specifically, has also been reported as a treatment  
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15 438 for arrhythmia and for lymphatic dysplasia, each of which can be isolated or comorbid conditions in  
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17 440 children with RASopathies and cardiomyopathy, further supporting the efficacy of targeted therapy  
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19 441 in RASopathy-associated conditions (Meisner et al., 2021; Dori et al., 2020; Nakano et al., 2022).  
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21 442 However, the absence of clinical trials or large studies evaluating the risk and benefits of these  
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23 443 drugs limits their use in clinical practice.

24 444 ~~Treatment of RASopathies with therapies targeting the RAS/MAPK cascade (in NS) or the~~  
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26 445 ~~PI3K/AKT/mTor pathway (in NSML) are limited to case reports suggesting a beneficial effect of~~  
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28 446 ~~these therapeutic approaches in improving clinical status and resulting in LVH regression~~  
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30 447 ~~(Andelfinger et al., 2019; Marin et al., 2011; However, the absence of clinical trials or large studies~~  
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32 448 ~~evaluating the risk and benefits of these drugs limits their use in clinical practice.~~

## 32 449 CONCLUSIONS AND PERSPECTIVES

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35 450 As this review demonstrates, the cardiovascular phenotype associated with RASopathies has  
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37 451 expanded far beyond the original descriptions of pulmonary valve stenosis by Dr. Jaqueline Noonan  
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39 452 in 1968 and hypertrophic cardiomyopathy by Hirsch *et al* in 1975 (Noonan, 1968; Hirsch et al.,  
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41 453 1975). Yet, we still can appreciate the importance of these two cardiac findings with respect to  
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43 454 disease burden and morbidity among individuals with RASopathy disorders. Our understanding of  
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45 455 the phenotypes associated with RAS pathway gene variants has continued to expand at a rapid pace  
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47 457 with a great deal of interest in the associated cardiovascular phenotypes based on the specific gene  
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49 458 (Pierpont & Digilio, 2018). The common and overlapping cardiovascular phenotypes among all of  
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51 459 the RASopathies underscores the recognized common pathophysiology of this group of conditions  
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53 460 which generally speaking results in activating RAS/MAPK signal transduction. Still, there are  
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55 461 clearly systemic—morphologic and other organ system—differences that are clear when one  
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57 462 compares genotype groups. For example, patients with *PTPN11*-associated Noonan syndrome are  
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59 463 distinguishable from patients with *RAF1*-associated Noonan syndrome, and their risk for  
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464 cardiovascular disease also diverge slightly, with *PTPN11* conferring higher risk for pulmonary  
465 valve stenosis and less risk for hypertrophic cardiomyopathy, the converse being true for *RAF1*.  
Determination and understanding of genotype is not only important for counselling a family of an

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466 infant with a new diagnosis of a RASopathy condition but is also critical for their clinical prognosis  
467 with respect to cardiac disease, neurodevelopment and other organ system involvement over the  
468 lifetime of the patient.

469 Equally important is our better understanding of the prevalence of RASopathy disorders in  
470 patients with these common cardiac phenotypes, individually and in various combinations:  
471 pulmonary valve stenosis, infantile hypertrophic cardiomyopathy, polyvalvular dysplasia, and  
472 incidentally detected coronary artery ectasia. While pediatric cardiologists have, as a specialty,  
473 become quite knowledgeable about common syndromic forms of congenital heart disease and the  
474 relevance of genetic diagnosis in patients with certain types of congenital heart defects and  
475 cardiomyopathy, much more is still to be learned about how to use genetic diagnosis to improve  
476 clinical outcomes. While barriers still exist to collecting genetic information from medical records  
477 datasets, future research will depend on the ability to determine hospital and surgical outcomes  
478 based on genetic etiology of diseases such as RASopathies. This data collection and analysis is  
479 necessary for understanding outcomes for individuals with RASopathies and providing evidence-  
480 based precision care. Better understanding of new cardiovascular phenotypes is another area that  
481 warrants further investigation. While treatments of pulmonary valve stenosis or hypertrophic  
482 cardiomyopathy are well studied, and clinical guidelines established, mildly dysplastic heart valves  
483 and coronary ectasia/aneurysm attributable to RAS pathway variants are two examples of  
484 cardiovascular disease for which there are no standards of care for monitoring or treatment. The  
485 prevalence and associated morbidity of these findings is entirely unknown.

486 Efforts to improve our understanding of genotype-cardiac phenotype correlations in  
487 RASopathies will be critical for optimal medical and surgical management. Genotype can for  
488 example to some degree predict risk for associated bleeding disorders, lymphatic dysplasia,  
489 malignancy and other comorbidities that can have significant impact on outcome of a cardiac  
490 procedure, and on quality of life for the individual. While the collective literature on RASopathies  
491 and the associated cardiovascular features is expansive, large systematic population-based and long-  
492 term outcomes research are lacking, and especially needed to truly understand how genotype can  
493 best inform clinical care in patients with RASopathy-associated cardiovascular disease.

494 Of great interest is the application of FDA-approved and investigational RAS/MAPK  
495 pathway inhibitors, such as trametinib and sirolimus, in the treatment of hypertrophic  
496 cardiomyopathy and other morbid complications of RASopathies, such as lymphatic disease and  
497 malignancy.

498 Understanding of the influence of various gain-of function variants in the RAS/MAPK  
499 pathway will be critical to understand the utility and efficacy of these treatments in children with



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3 500 Noonan syndrome and related RASopathies. While only a handful of publications exist that  
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5 501 describe isolated experiences with these pharmacologic agents, they are being used widely  
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7 502 throughout the United States, Canada and Europe under investigational/compassionate use or off-  
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9 503 label. Real-world collection of this collective experience is likely to shape the next decade of  
10 504 clinical research in RASopathy conditions and will be a paradigm of personalized medicine for  
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12 505 monogenic disease in the modern era.

### 13 506 14 15 16 507 **CONFLICT OF INTEREST**

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18 508  
19 509 The authors declare no conflict of interests.  
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### 22 510 23 24 511 **DATA AVAILABILITY STATEMENT**

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28 513 Data sharing is not applicable to this article as no new data were created or analyzed in this study.  
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### 33 34 516 **REFERENCES**

- 35 517  
36 518 Alexander, P. M. A., Nugent, A. W., Daubeney, P. E. F., Lee, K. J., Sleeper, L. A., Schuster, T.,  
37  
38 519 Turner, C., Davis, A. M., Semsarian, C., Colan, S. D., Robertson, T., Ramsay, J., Justo, R., Sholler,  
39  
40 520 G. F., King, I., Weintraub, R. G., & National Australian Childhood Cardiomyopathy Study. (2018).  
41  
42 521 Long-Term Outcomes of Hypertrophic Cardiomyopathy Diagnosed During Childhood: Results  
43 522 From a National Population-Based Study. *Circulation*, *138*(1), 29–36.  
44  
45 523 <https://doi.org/10.1161/CIRCULATIONAHA.117.028895>  
46  
47 524 Allanson, J. E., Annerén, G., Aoki, Y., Armour, C. M., Bondeson, M.-L., Cave, H., Gripp, K. W.,  
48  
49 525 Kerr, B., Nystrom, A.-M., Sol-Church, K., Verloes, A., & Zenker, M. (2011). Cardio-facio-  
50  
51 526 cutaneous syndrome: Does genotype predict phenotype? *American Journal of Medical Genetics*.  
52 527 *Part C, Seminars in Medical Genetics*, *157C*(2), 129–135. <https://doi.org/10.1002/ajmg.c.30295>  
53  
54  
55 528 Andelfinger, G., Marquis, C., Raboisson, M.-J., Théoret, Y., Waldmüller, S., Wiegand, G., Gelb, B.  
56  
57 529 D., Zenker, M., Delrue, M.-A., & Hofbeck, M. (2019). Hypertrophic Cardiomyopathy in Noonan  
58 530 Syndrome Treated by MEK-Inhibition. *Journal of the American College of Cardiology*, *73*(17),  
59  
60 531 2237–2239. <https://doi.org/10.1016/j.jacc.2019.01.066>

- 1  
2  
3 532 Aoki, Y., Niihori, T., Banjo, T., Okamoto, N., Mizuno, S., Kurosawa, K., Ogata, T., Takada, F.,  
4  
5 533 Yano, M., Ando, T., Hoshika, T., Barnett, C., Ohashi, H., Kawame, H., Hasegawa, T., Okutani, T.,  
6  
7 534 Nagashima, T., Hasegawa, S., Funayama, R., ... Matsubara, Y. (2013). Gain-of-Function Mutations  
8  
9 535 in RIT1 Cause Noonan Syndrome, a RAS/MAPK Pathway Syndrome. *The American Journal of*  
10 536 *Human Genetics*, 93(1), 173–180. <https://doi.org/10.1016/j.ajhg.2013.05.021>  
11  
12 537 Aoki, Y., Niihori, T., Inoue, S., & Matsubara, Y. (2016). Recent advances in RASopathies. *Journal*  
13 538 *of Human Genetics*, 61(1), 33–39. <https://doi.org/10.1038/jhg.2015.114>  
14  
15  
16 539 Armour, C. M., & Allanson, J. E. (2007). Further delineation of cardio-facio-cutaneous syndrome:  
17 540 Clinical features of 38 individuals with proven mutations. *Journal of Medical Genetics*, 45(4), 249–  
18 541 254. <https://doi.org/10.1136/jmg.2007.054460>  
19  
20  
21  
22 542 Artoni, A., Selicorni, A., Passamonti, S. M., Lecchi, A., Bucciarelli, P., Cerutti, M., Cianci, P.,  
23 543 Gianniello, F., & Martinelli, I. (2014). Hemostatic abnormalities in Noonan  
24 544 syndrome. *Pediatrics*, 133(5), e1299–e1304. <https://doi.org/10.1542/peds.2013-3251>  
25  
26  
27  
28 545 Authors/Task Force members, Elliott, P. M., Anastasakis, A., Borger, M. A., Borggrefe, M.,  
29 546 Cecchi, F., Charron, P., Hagege, A. A., Lafont, A., Limongelli, G., Mahrholdt, H., McKenna, W. J.,  
30 547 Mogensen, J., Nihoyannopoulos, P., Nistri, S., Pieper, P. G., Pieske, B., Rapezzi, C., Rutten, F. H.,  
31 548 ... Watkins, H. (2014). 2014 ESC Guidelines on diagnosis and management of hypertrophic  
32 549 cardiomyopathy: The Task Force for the Diagnosis and Management of Hypertrophic  
33 550 Cardiomyopathy of the European Society of Cardiology (ESC). *European Heart Journal*, 35(39),  
34 551 2733–2779. <https://doi.org/10.1093/eurheartj/ehu284>  
35  
36  
37  
38  
39  
40  
41 552 [Baumgartner, H., De Backer, J., Babu-Narayan, S. V., Budts, W., Chessa, M., Diller, G.-P., Lung,](#)  
42  
43 553 [B., Kluin, J., Lang, I. M., Meijboom, F., Moons, P., Mulder, B. J. M., Oechslin, E., Roos-Hesselink,](#)  
44  
45 554 [J. W., Schwerzmann, M., Sondergaard, L., Zeppenfeld, K., & ESC Scientific Document Group.](#)  
46 555 [\(2021\). 2020 ESC Guidelines for the management of adult congenital heart disease. \*European\*](#)  
47  
48 556 [Heart Journal](#), 42(6), 563–645. <https://doi.org/10.1093/eurheartj/ehaa554>  
49  
50  
51 557 Bell, J. M., Considine, E. M., McCallen, L. M., & Chatfield, K. C. (2021). The Prevalence of  
52 558 Noonan Spectrum Disorders in Pediatric Patients with Pulmonary Valve Stenosis. *The Journal of*  
53 559 *Pediatrics*, 234, 134–141.e5. <https://doi.org/10.1016/j.jpeds.2021.03.050>  
54  
55  
56 560 Briggs, B. J., & Dickerman, J. D. (2012). Bleeding disorders in Noonan syndrome. *Pediatric blood*  
57  
58 561 *& cancer*, 58(2), 167–172. <https://doi.org/10.1002/pbc.23358>  
59  
60

1  
2  
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50  
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54  
55  
56  
57  
58  
59  
60

- 562 Burch, M., Sharland, M., Shinebourne, E., Smith, G., Patton, M., & McKenna, W. (1993).  
563 Cardiologic abnormalities in Noonan syndrome: Phenotypic diagnosis and echocardiographic  
564 assessment of 118 patients. *Journal of the American College of Cardiology*, 22(4), 1189–1192.  
565 [https://doi.org/10.1016/0735-1097\(93\)90436-5](https://doi.org/10.1016/0735-1097(93)90436-5)
- 566 Calcagni, G., Baban, A., De Luca, E., Leonardi, B., Pongiglione, G., & Digilio, M. C. (2016).  
567 Coronary artery ectasia in Noonan syndrome: Report of an individual with SOS1 mutation and  
568 literature review. *American Journal of Medical Genetics. Part A*, 170(3), 665–669.  
569 <https://doi.org/10.1002/ajmg.a.37505>
- 570 Calcagni, G., Gagliostro, G., Limongelli, G., Unolt, M., De Luca, E., Digilio, M. C., Baban, A.,  
571 Albanese, S. B., Ferrero, G. B., Baldassarre, G., Agnoletti, G., Banaudi, E., Marek, J., Kaski, J. P.,  
572 Tuo, G., Marasini, M., Cairello, F., Madrigali, A., Pacileo, G., ... Versacci, P. (2020). Atypical  
573 cardiac defects in patients with RASopathies: Updated data on CARNET study. *Birth Defects  
574 Research*, 112(10), 725–731. <https://doi.org/10.1002/bdr2.1670>
- 575 Calcagni, G., Limongelli, G., D'Ambrosio, A., Gesualdo, F., Digilio, M. C., Baban, A., Albanese,  
576 S. B., Versacci, P., De Luca, E., Ferrero, G. B., Baldassarre, G., Agnoletti, G., Banaudi, E., Marek,  
577 J., Kaski, J. P., Tuo, G., Russo, M. G., Pacileo, G., Milanese, O., ... Marino, B. (2017). Cardiac  
578 defects, morbidity and mortality in patients affected by RASopathies. CARNET study results.  
579 *International Journal of Cardiology*, 245, 92–98. <https://doi.org/10.1016/j.ijcard.2017.07.068>
- 580 Cerrato, F., Pacileo, G., Limongelli, G., Gagliardi, M. G., Santoro, G., Digilio, M. C., Di Salvo, G.,  
581 Ardorisio, R., Miele, T., & Calabrò, R. (2008). A standard echocardiographic and tissue Doppler  
582 study of morphological and functional findings in children with hypertrophic cardiomyopathy  
583 compared to those with left ventricular hypertrophy in the setting of Noonan and LEOPARD  
584 syndromes. *Cardiology in the Young*, 18(6), 575–580. <https://doi.org/10.1017/S104795110800320X>
- 585 Chinton, J., Huckstadt, V., Mucciolo, M., Lepri, F., Novelli, A., Gravina, L. P., & Obregon, M. G.  
586 (2020). Providing more evidence on LZTR1 variants in Noonan syndrome patients. *American  
587 Journal of Medical Genetics Part A*, 182(2), 409–414. <https://doi.org/10.1002/ajmg.a.61445>
- 588 Colquitt, J. L., & Noonan, J. A. (2014). Cardiac findings in Noonan syndrome on long-term follow-  
589 up. *Congenital Heart Disease*, 9(2), 144–150. <https://doi.org/10.1111/chd.12102>
- 590 Cordeddu, V., Di Schiavi, E., Pennacchio, L. A., Ma'ayan, A., Sarkozy, A., Fodale, V., Cecchetti,  
591 S., Cardinale, A., Martin, J., Schackwitz, W., Lipzen, A., Zampino, G., Mazzanti, L., Digilio, M. C.,  
592 Martinelli, S., Flex, E., Lepri, F., Bartholdi, D., Kutsche, K., ... Tartaglia, M. (2009). Mutation of

- 1  
2  
3 593 SHOC2 promotes aberrant protein N-myristoylation and causes Noonan-like syndrome with loose  
4 anagen hair. *Nature Genetics*, *41*(9), 1022–1026. <https://doi.org/10.1038/ng.425>  
5 594  
6  
7 595 Cordeddu, V., Yin, J. C., Gunnarsson, C., Virtanen, C., Drunat, S., Lepri, F., De Luca, A., Rossi,  
8 C., Ciolfi, A., Pugh, T. J., Bruselles, A., Priest, J. R., Pennacchio, L. A., Lu, Z., Danesh, A.,  
9 596 Quevedo, R., Hamid, A., Martinelli, S., Pantaleoni, F., ... Tartaglia, M. (2015). Activating  
10 Mutations Affecting the Dbl Homology Domain of SOS2 Cause Noonan Syndrome. *Human*  
11 597 *Mutation*, *36*(11), 1080–1087. <https://doi.org/10.1002/humu.22834>  
12 598  
13  
14 599 Cornwall, J. W., Green, R. S., Nielsen, J. C., & Gelb, B. D. (2014). Frequency of aortic dilation in  
15 600 Noonan syndrome. *The American Journal of Cardiology*, *113*(2), 368–371.  
16 601 <https://doi.org/10.1016/j.amjcard.2013.09.034>  
17 602  
18  
19  
20 603 Delogu, A. B., Blandino, R., Leoni, C., Tartaglia, M., & Zampino, G. (2022). RASopathies and  
21 sigmoid-shaped ventricular septum morphology: Evidence of a previously unappreciated cardiac  
22 604 phenotype. *Pediatric Research*. <https://doi.org/10.1038/s41390-022-02184-8>  
23 605  
24  
25  
26 606 Di Candia, F., Marchetti, V., Cirillo, F., Di Minno, A., Rosano, C., Pagano, S., Siano, M. A., Falco,  
27 M., Assunto, A., Boccia, G., Magliacane, G., Pinna, V., De Luca, A., Tartaglia, M., Di Minno, G.,  
28 607 Strisciuglio, P., & Melis, D. (2021). RASopathies and hemostatic abnormalities: key role of platelet  
29 dysfunction. *Orphanet journal of rare diseases*, *16*(1), 499. [https://doi.org/10.1186/s13023-021-](https://doi.org/10.1186/s13023-021-02122-7)  
30 608 [02122-7](https://doi.org/10.1186/s13023-021-02122-7)  
31 609  
32  
33  
34 610 Digilio, M. C., Lepri, F., Baban, A., Dentici, M. L., Versacci, P., Capolino, R., Ferese, R., De Luca,  
35 611 A., Tartaglia, M., Marino, B., & Dallapiccola, B. (2010). RASopathies: Clinical Diagnosis in the  
36 612 First Year of Life. *Molecular Syndromology*, *1*(6), 282–289. <https://doi.org/10.1159/000331266>  
37 613  
38  
39  
40 614 Digilio, M. C., Lepri, F., Baban, A., Dentici, M. L., Versacci, P., Capolino, R., Ferese, R., De Luca,  
41 615 A., Tartaglia, M., Marino, B., & Dallapiccola, B. (2011). RASopathies: Clinical Diagnosis in the  
42 616 First Year of Life. *Molecular Syndromology*, *1*(6), 282–289. <https://doi.org/10.1159/000331266>  
43 617  
44  
45  
46 618 Digilio, M. C., Marino, B., Giannotti, A., & Dallapiccola, B. (1997). Noonan syndrome with  
47 619 cardiac left-sided obstructive lesions. *Human Genetics*, *99*(2), 289.  
48 <https://doi.org/10.1007/s004390050357>  
49 620  
50  
51  
52 621 Digilio, M. C., Marino, B., Picchio, F., Prandstraller, D., Toscano, A., Giannotti, A., &  
53 622 Dallapiccola, B. (1998). Noonan syndrome and aortic coarctation. *American Journal of Medical*  
54 *Genetics*, *80*(2), 160–162.  
55  
56  
57  
58  
59  
60

1  
2  
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4  
5  
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47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 623 Digilio, M. C., Marino, B., Sarkozy, A., Versacci, P., & Dallapiccola, B. (2009). The Heart in Ras-  
 624 MAPK Pathway Disorders. *Noonan Syndrome and Related Disorders - A Matter of Deregulated*  
 625 *Ras Signaling*, *17*, 109–118. <https://doi.org/10.1159/000164847>
- 626 Digilio, M. C., Romana Lepri, F., Dentici, M. L., Henderson, A., Baban, A., Roberti, M. C.,  
 627 Capolino, R., Versacci, P., Surace, C., Angioni, A., Tartaglia, M., Marino, B., & Dallapiccola, B.  
 628 (2013). Atrioventricular canal defect in patients with RASopathies. *European Journal of Human*  
 629 *Genetics: EJHG*, *21*(2), 200–204. <https://doi.org/10.1038/ejhg.2012.145>
- 630 Digilio, M., & Marino, B. (2001). Clinical manifestations of Noonan syndrome. *Images in*  
 631 *Paediatric Cardiology*, *3*(2), 19–30.
- 632 [Dori, Y., Smith, C., Pinto, E., Snyder, K., March, M. E., Hakonarson, H., & Belasco, J. \(2020\).](#)  
 633 [Severe Lymphatic Disorder Resolved With MEK Inhibition in a Patient With Noonan Syndrome](#)  
 634 [and SOS1 Mutation. \*Pediatrics\*, \*146\*\(6\), e20200167. <https://doi.org/10.1542/peds.2020-0167>](#)
- 635 Gajarski, R., Naftel, D. C., Pahl, E., Alejos, J., Pearce, F. B., Kirklin, J. K., Zamberlan, M.,  
 636 Dipchand, A. I., & Pediatric Heart Transplant Study Investigators. (2009). Outcomes of pediatric  
 637 patients with hypertrophic cardiomyopathy listed for transplant. *The Journal of Heart and Lung*  
 638 *Transplantation: The Official Publication of the International Society for Heart Transplantation*,  
 639 *28*(12), 1329–1334. <https://doi.org/10.1016/j.healun.2009.05.028>
- 640 Gelb, B. D., & Tartaglia, M. (2011). RAS signaling pathway mutations and hypertrophic  
 641 cardiomyopathy: Getting into and out of the thick of it. *The Journal of Clinical Investigation*,  
 642 *121*(3), 844–847. <https://doi.org/10.1172/JCI46399>
- 643 Gripp, K. W., Morse, L. A., Axelrad, M., Chatfield, K. C., Chidekel, A., Dobyns, W., Doyle, D.,  
 644 Kerr, B., Lin, A. E., Schwartz, D. D., Sibbles, B. J., Siegel, D., Shankar, S. P., Stevenson, D. A.,  
 645 Thacker, M. M., Weaver, K. N., White, S. M., & Rauen, K. A. (2019). Costello syndrome: Clinical  
 646 phenotype, genotype, and management guidelines. *American Journal of Medical Genetics, Part A*,  
 647 *179*(9), 1725–1744. <https://doi.org/10.1002/ajmg.a.61270>
- 648 Hemmati, P., Dearani, J. A., Daly, R. C., King, K. S., Ammash, N. M., Cetta, F., & Schaff, H. V.  
 649 (2019). Early Outcomes of Cardiac Surgery in Patients with Noonan Syndrome. *Seminars in*  
 650 *Thoracic and Cardiovascular Surgery*, *31*(3), 507–513.  
 651 <https://doi.org/10.1053/j.semtcvs.2018.12.004>

1  
2  
3  
4  
5  
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53  
54  
55  
56  
57  
58  
59  
60

652 Hirsch, H. D., Gelband, H., Garcia, O., Gottlieb, S., & Tamer, D. M. (1975). Rapidly progressive  
653 obstructive cardiomyopathy in infants with Noonan's syndrome. Report of two  
654 cases. *Circulation*, 52(6), 1161–1165. <https://doi.org/10.1161/01.cir.52.6.1161>

655 [Holzmann, J., Tibby, S. M., Rosenthal, E., Qureshi, S., Morgan, G., & Krasemann, T. \(2018\).  
656 Results of balloon pulmonary valvoplasty in children with Noonan's syndrome. \*Cardiology in the  
657 young\*, 28\(5\), 647–652. <https://doi.org/10.1017/S1047951117002827>](#)

658 Jhang, W. K., Choi, J.-H., Lee, B. H., Kim, G.-H., & Yoo, H.-W. (2016). Cardiac Manifestations  
659 and Associations with Gene Mutations in Patients Diagnosed with RASopathies. *Pediatric  
660 Cardiology*, 37(8), 1539–1547. <https://doi.org/10.1007/s00246-016-1468-6>

661 Kauffman, H., Ahrens-Nicklas, R. C., Calderon-Anyosa, R. J. C., Ritter, A. L., Lin, K. Y., Rossano,  
662 J. W., Quartermain, M. D., & Banerjee, A. (2021). Genotype-phenotype association by  
663 echocardiography offers incremental value in patients with Noonan Syndrome with Multiple  
664 Lentigines. *Pediatric Research*, 90(2), 444–451. <https://doi.org/10.1038/s41390-020-01292-7>

665 Keilhack, H., David, F. S., McGregor, M., Cantley, L. C., & Neel, B. G. (2005). Diverse  
666 biochemical properties of Shp2 mutants. Implications for disease phenotypes. *The Journal of  
667 Biological Chemistry*, 280(35), 30984–30993. <https://doi.org/10.1074/jbc.M504699200>

668 Kobayashi, T., Aoki, Y., Niihori, T., Cavé, H., Verloes, A., Okamoto, N., Kawame, H., Fujiwara, I.,  
669 Takada, F., Ohata, T., Sakazume, S., Ando, T., Nakagawa, N., Lapunzina, P., Meneses, A. G.,  
670 Gillessen-Kaesbach, G., Wiczorek, D., Kurosawa, K., Mizuno, S., ... Matsubara, Y. (2010).  
671 Molecular and clinical analysis of *RAF1* in Noonan syndrome and related disorders:  
672 Dephosphorylation of serine 259 as the essential mechanism for mutant activation. *Human  
673 Mutation*, 31(3), 284–294. <https://doi.org/10.1002/humu.21187>

674 Komatsuzaki, S., Aoki, Y., Niihori, T., Okamoto, N., Hennekam, R. C. M., Hopman, S., Ohashi, H.,  
675 Mizuno, S., Watanabe, Y., Kamasaki, H., Kondo, I., Moriyama, N., Kurosawa, K., Kawame, H.,  
676 Okuyama, R., Imaizumi, M., Rikiishi, T., Tsuchiya, S., Kure, S., & Matsubara, Y. (2010). Mutation  
677 analysis of the SHOC2 gene in Noonan-like syndrome and in hematologic malignancies. *Journal of  
678 Human Genetics*, 55(12), 801–809. <https://doi.org/10.1038/jhg.2010.116>

679 Lauriol, J., & Kontaridis, M. I. (2011). PTPN11-associated mutations in the heart: Has LEOPARD  
680 changed Its RASpots? *Trends in Cardiovascular Medicine*, 21(4), 97–104.  
681 <https://doi.org/10.1016/j.tcm.2012.03.006>

1

2

3

4

5

6

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46

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50

51

52

53

54

55

56

57

58

59

60

- 682 Leoni, C., Blandino, R., Delogu, A. B., De Rosa, G., Onesimo, R., Verusio, V., Marino, M. V.,  
683 Lanza, G. A., Rigante, D., Tartaglia, M., & Zampino, G. (2022). Genotype-cardiac phenotype  
684 correlations in a large single-center cohort of patients affected by RASopathies: Clinical  
685 implications and literature review. *American Journal of Medical Genetics Part A*, *188*(2), 431–445.  
686 <https://doi.org/10.1002/ajmg.a.62529>
- 687 Levin, M. D., Saitta, S. C., Gripp, K. W., Wenger, T. L., Ganesh, J., Kalish, J. M., Epstein, M. R.,  
688 Smith, R., Czosek, R. J., Ware, S. M., Goldenberg, P., Myers, A., Chatfield, K. C., Gillespie, M. J.,  
689 Zackai, E. H., & Lin, A. E. (2018). Nonreentrant atrial tachycardia occurs independently of  
690 hypertrophic cardiomyopathy in RASopathy patients. *American Journal of Medical Genetics. Part*  
691 *A*, *176*(8), 1711–1722. <https://doi.org/10.1002/ajmg.a.38854>
- 692 Limongelli, G., Adorisio, R., Baggio, C., Bauce, B., Biagini, E., Castelletti, S., Favilli, S., Imazio,  
693 M., Lioncino, M., Merlo, M., Monda, E., Olivotto, I., Parisi, V., Pelliccia, F., Basso, C., Sinagra,  
694 G., Indolfi, C., Autore, C., WG on Cardiomyopathies of SIC (Società Italiana di Cardiologia), &  
695 WG on Cardiomyopathies of SICPed (Società Italiana di Cardiologia Pediatrica). (2022). Diagnosis  
696 and Management of Rare Cardiomyopathies in Adult and Paediatric Patients. A Position Paper of  
697 the Italian Society of Cardiology (SIC) and Italian Society of Paediatric Cardiology (SICP).  
698 *International Journal of Cardiology*, *357*, 55–71. <https://doi.org/10.1016/j.ijcard.2022.03.050>
- 699 Limongelli, G., Monda, E., Tramonte, S., Gragnano, F., Masarone, D., Frisso, G., Esposito, A.,  
700 Gravino, R., Ammendola, E., Salerno, G., Rubino, M., Caiazza, M., Russo, M., Calabrò, P., Elliott,  
701 P. M., & Pacileo, G. (2020). Prevalence and clinical significance of red flags in patients with  
702 hypertrophic cardiomyopathy. *International Journal of Cardiology*, *299*, 186–191.  
703 <https://doi.org/10.1016/j.ijcard.2019.06.073>
- 704 Limongelli, G., Pacileo, G., Marino, B., Digilio, M. C., Sarkozy, A., Elliott, P., Versacci, P.,  
705 Calabro, P., De Zorzi, A., Di Salvo, G., Syrris, P., Patton, M., McKenna, W. J., Dallapiccola, B., &  
706 Calabro, R. (2007). Prevalence and clinical significance of cardiovascular abnormalities in patients  
707 with the LEOPARD syndrome. *The American Journal of Cardiology*, *100*(4), 736–741.  
708 <https://doi.org/10.1016/j.amjcard.2007.03.093>
- 709 Limongelli, G., Sarkozy, A., Pacileo, G., Calabrò, P., Digilio, M. C., Maddaloni, V., Gagliardi, G.,  
710 Di Salvo, G., Iacomino, M., Marino, B., Dallapiccola, B., & Calabrò, R. (2008). Genotype-  
711 phenotype analysis and natural history of left ventricular hypertrophy in LEOPARD syndrome.  
712 *American Journal of Medical Genetics. Part A*, *146A*(5), 620–628.  
713 <https://doi.org/10.1002/ajmg.a.32206>

- 1  
2  
3 714 Lin, A. E., Alexander, M. E., Colan, S. D., Kerr, B., Rauen, K. A., Noonan, J., Baffa, J., Hopkins,  
4  
5 715 E., Sol-Church, K., Limongelli, G., Digilio, M. C., Marino, B., Innes, A. M., Aoki, Y., Silberbach,  
6  
7 716 M., Delrue, M.-A., White, S. M., Hamilton, R. M., O'Connor, W., ... Gripp, K. W. (2011). Clinical,  
8  
9 717 pathological, and molecular analyses of cardiovascular abnormalities in Costello syndrome: A  
10 718 Ras/MAPK pathway syndrome. *American Journal of Medical Genetics Part A*, 155(3), 486–507.  
11  
12 719 <https://doi.org/10.1002/ajmg.a.33857>  
13  
14 720 Lin, A. E., Basson, C. T., Goldmuntz, E., Magoulas, P. L., McDermott, D. A., McDonald-McGinn,  
15  
16 721 D. M., McPherson, E., Morris, C. A., Noonan, J., Nowak, C., Pierpont, M. E., Pyeritz, R. E., Rope,  
17  
18 722 A. F., Zackai, E., & Pober, B. R. (2008). Adults with genetic syndromes and cardiovascular  
19 723 abnormalities: Clinical history and management. *Genetics in Medicine*, 10(7), 469–494.  
20  
21 724 <https://doi.org/10.1097/GIM.0b013e3181772111>  
22  
23 725 Linglart, L., & Gelb, B. D. (2020). Congenital heart defects in Noonan syndrome: Diagnosis,  
24 726 management, and treatment. *American Journal of Medical Genetics. Part C, Seminars in Medical*  
25 727 *Genetics*, 184(1), 73–80. <https://doi.org/10.1002/ajmg.c.31765>  
26  
27 728  
28  
29 728 Lioncino, M., Monda, E., Verrillo, F., Moscarella, E., Calcagni, G., Drago, F., Marino, B., Digilio,  
30  
31 729 M. C., Putotto, C., Calabrò, P., Russo, M. G., Roberts, A. E., Gelb, B. D., Tartaglia, M., &  
32  
33 730 Limongelli, G. (2022). Hypertrophic Cardiomyopathy in RASopathies: Diagnosis, Clinical  
34 731 Characteristics, Prognostic Implications, and Management. *Heart Failure Clinics*, 18(1), 19–29.  
35 732  
36 732 <https://doi.org/10.1016/j.hfc.2021.07.004>  
37  
38  
39 733 Marin, T. M., Keith, K., Davies, B., Conner, D. A., Guha, P., Kalaitzidis, D., Wu, X., Lauriol, J.,  
40 734 Wang, B., Bauer, M., Bronson, R., Franchini, K. G., Neel, B. G., & Kontaridis, M. I. (2011).  
41 735 Rapamycin reverses hypertrophic cardiomyopathy in a mouse model of LEOPARD syndrome–  
42 736 associated PTPN11 mutation. *Journal of Clinical Investigation*, 121(3), 1026–1043.  
43 737  
44 737 <https://doi.org/10.1172/JCI44972>  
45  
46  
47  
48 738 Marino, B., Digilio, M. C., Toscano, A., Giannotti, A., & Dallapiccola, B. (1999). Congenital heart  
49 739 diseases in children with Noonan syndrome: An expanded cardiac spectrum with high prevalence of  
50 740 atrioventricular canal. *The Journal of Pediatrics*, 135(6), 703–706. [https://doi.org/10.1016/s0022-3476\(99\)70088-0](https://doi.org/10.1016/s0022-3476(99)70088-0)  
51 741  
52  
53 742  
54  
55 742 Marino, B., Gagliardi, M. G., Digilio, M. C., Polletta, B., Grazioli, S., Agostino, D., Giannotti, A.,  
56 743 & Dallapiccola, B. (1995). Noonan syndrome: Structural abnormalities of the mitral valve causing  
57 744 subaortic obstruction. *European Journal of Pediatrics*, 154(12), 949–952.  
58 745  
59 745 <https://doi.org/10.1007/BF01958636>  
60



1  
2  
3  
4  
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7  
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48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 746 Matalon, D. R., Stevenson, D. A., Bhoj, E. J., Santani, A. B., Keena, B., Cohen, M. S., Lin, A. E.,  
747 Sheppard, S. E., & Zackai, E. H. (2021). Congenital polyvalvular disease expands the cardiac  
748 phenotype of the RASopathies. *American Journal of Medical Genetics Part A*, 185(5), 1486–1493.  
749 <https://doi.org/10.1002/ajmg.a.62146>
- 750 McCallen, L. M., Ameduri, R. K., Denfield, S. W., Dodd, D. A., Everitt, M. D., Johnson, J. N., Lee,  
751 T. M., Lin, A. E., Lohr, J. L., May, L. J., Pierpont, M. E., Stevenson, D. A., & Chatfield, K. C.  
752 (2019). Cardiac transplantation in children with Noonan syndrome. *Pediatric Transplantation*,  
753 23(6), e13535. <https://doi.org/10.1111/ptr.13535>
- 754 McCrindle, B. W. (1994). Independent predictors of long-term results after balloon pulmonary  
755 valvuloplasty. Valvuloplasty and Angioplasty of Congenital Anomalies (VACA) Registry  
756 Investigators. *Circulation*, 89(4), 1751–1759. <https://doi.org/10.1161/01.CIR.89.4.1751>
- 757 [Meisner, J. K., Bradley, D. J., & Russell, M. W. \(2021\). Molecular Management of Multifocal](#)  
758 [Atrial Tachycardia in Noonan's Syndrome With MEK1/2 Inhibitor Trametinib. \*Circulation.\*](#)  
759 [\*Genomic and precision medicine\*, 14\(5\), e003327. <https://doi.org/10.1161/CIRCGEN.121.003327>](#)
- 760 Monda, E., Lioncino, M., Pacileo, R., Rubino, M., Cirillo, A., Fusco, A., Esposito, A., Verrillo, F.,  
761 Di Fraia, F., Mauriello, A., Tessitore, V., Caiazza, M., Cesaro, A., Calabrò, P., Russo, M. G., &  
762 Limongelli, G. (2021). Advanced Heart Failure in Special Population-Pediatric Age. *Heart Failure*  
763 *Clinics*, 17(4), 673–683. <https://doi.org/10.1016/j.hfc.2021.05.011>
- 764 Monda, E., Lioncino, M., Palmiero, G., Franco, F., Rubino, M., Cirillo, A., Verrillo, F., Fusco, A.,  
765 Caiazza, M., Mazzella, M., Moscarella, E., Dongiglio, F., Sepe, J., Pacileo, G., Calabrò, P., &  
766 Limongelli, G. (2022). Bisoprolol for treatment of symptomatic patients with obstructive  
767 hypertrophic cardiomyopathy. The BASIC (bisoprolol AS therapy in hypertrophic cardiomyopathy)  
768 study. *International Journal of Cardiology*, 354, 22–28.  
769 <https://doi.org/10.1016/j.ijcard.2022.03.013>
- 770 Monda, E., Lioncino, M., Rubino, M., Caiazza, M., Cirillo, A., Fusco, A., Pacileo, R., Fimiani, F.,  
771 Amodio, F., Borrelli, N., Colonna, D., D'Onofrio, B., Frisso, G., Drago, F., Castelletti, S., Sarubbi,  
772 B., Calabrò, P., Russo, M. G., & Limongelli, G. (2022). The Risk of Sudden Unexpected Cardiac  
773 Death in Children: Epidemiology, Clinical Causes, and Prevention. *Heart Failure Clinics*, 18(1),  
774 115–123. <https://doi.org/10.1016/j.hfc.2021.07.002>
- 775 Monda, E., Rubino, M., Lioncino, M., Di Fraia, F., Pacileo, R., Verrillo, F., Cirillo, A., Caiazza, M.,  
776 Fusco, A., Esposito, A., Fimiani, F., Palmiero, G., Pacileo, G., Calabrò, P., Russo, M. G., &

- 1  
2  
3 777 Limongelli, G. (2021). Hypertrophic Cardiomyopathy in Children: Pathophysiology, Diagnosis, and  
4 Treatment of Non-sarcomeric Causes. *Frontiers in Pediatrics*, 9, 632293.  
5 778 <https://doi.org/10.3389/fped.2021.632293>  
6 779  
7  
8  
9 780 Moran, A. M., & Colan, S. D. (1998). Verapamil therapy in infants with hypertrophic  
10 cardiomyopathy. *Cardiology in the Young*, 8(3), 310–319.  
11 781 <https://doi.org/10.1017/s1047951100006818>  
12 782  
13  
14  
15 783 Morgan, J. M., Coupe, M. O., Honey, M., & Miller, G. A. (1989). Aneurysms of the sinuses of  
16 Valsalva in Noonan's syndrome. *European Heart Journal*, 10(2), 190–193.  
17 784 <https://doi.org/10.1093/oxfordjournals.eurheartj.a059462>  
18 785  
19  
20  
21 786 [Mussa, A., Carli, D., Giorgio, E., Villar, A. M., Cardaropoli, S., Carbonara, C., Campagnoli, M. F.,](#)  
22 787 [Galletto, P., Palumbo, M., Olivieri, S., Isella, C., Andelfinger, G., Tartaglia, M., Botta, G., Brusco,](#)  
23 788 [A., Medico, E., & Ferrero, G. B. \(2021\). MEK Inhibition in a Newborn with \*RAF1\*-Associated](#)  
24 789 [Noonan Syndrome Ameliorates Hypertrophic Cardiomyopathy but Is Insufficient to Revert](#)  
25 790 [Pulmonary Vascular Disease. \*Genes\*, 13\(1\), 6. <https://doi.org/10.3390/genes13010006>](#)  
26 791  
27  
28  
29  
30 791 Myers, A., Bernstein, J. A., Brennan, M.-L., Curry, C., Esplin, E. D., Fisher, J., Homeyer, M.,  
31 792 Manning, M. A., Muller, E. A., Niemi, A.-K., Seaver, L. H., Hintz, S. R., & Hudgins, L. (2014).  
32 793 Perinatal features of the RASopathies: Noonan syndrome, cardiofaciocutaneous syndrome and  
33 794 Costello syndrome. *American Journal of Medical Genetics. Part A*, 164A(11), 2814–2821.  
34 795 <https://doi.org/10.1002/ajmg.a.36737>  
35 796  
36  
37  
38  
39 796 [Nakano, T. A., Rankin, A. W., Annam, A., Kulungowski, A. M., McCallen, L. M., Hill, L. R., &](#)  
40 797 [Chatfield, K. C. \(2022\). Trametinib for Refractory Chylous Effusions and Systemic Complications](#)  
41 798 [in Children with Noonan Syndrome. \*The Journal of pediatrics\*, S0022-3476\(22\)00479-6. Advance](#)  
42 799 [online publication. <https://doi.org/10.1016/j.jpeds.2022.05.030>](#)  
43 800  
44  
45  
46  
47 800 Noonan J. A. (1968). Hypertelorism with Turner phenotype. A new syndrome with associated  
48 801 congenital heart disease. *American journal of diseases of children (1960)*, 116(4), 373–380.  
49 802 <https://doi.org/10.1001/archpedi.1968.02100020377005>  
50 803  
51  
52  
53 803 Norrish, G., Field, E., Mcleod, K., Ilina, M., Stuart, G., Bhole, V., Uzun, O., Brown, E., Daubeney,  
54 804 P. E. F., Lota, A., Linter, K., Mathur, S., Bharucha, T., Kok, K. L., Adwani, S., Jones, C. B.,  
55 805 Reinhardt, Z., & Kaski, J. P. (2019). Clinical presentation and survival of childhood hypertrophic  
56 806 cardiomyopathy: A retrospective study in United Kingdom. *European Heart Journal*, 40(12), 986–  
57 807 993. <https://doi.org/10.1093/eurheartj/ehy798>  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
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49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 808 O'Connor, M. J., Miller, K., Shaddy, R. E., Lin, K. Y., Hanna, B. D., Ravishankar, C., & Rossano,  
809 J. W. (2018). Disopyramide use in infants and children with hypertrophic cardiomyopathy.  
810 *Cardiology in the Young*, 28(4), 530–535. <https://doi.org/10.1017/S1047951117002384>
- 811 Ommen, S. R., Mital, S., Burke, M. A., Day, S. M., Deswal, A., Elliott, P., Evanovich, L. L., Hung,  
812 J., Joglar, J. A., Kantor, P., Kimmelstiel, C., Kittleson, M., Link, M. S., Maron, M. S., Martinez, M.  
813 W., Miyake, C. Y., Schaff, H. V., Semsarian, C., & Sorajja, P. (2020). 2020 AHA/ACC Guideline  
814 for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy: A Report of the  
815 American College of Cardiology/American Heart Association Joint Committee on Clinical Practice  
816 Guidelines. *Circulation*, 142(25), e558–e631. <https://doi.org/10.1161/CIR.0000000000000937>
- 817 Pacileo, G., Calabrò, P., Limongelli, G., Santoro, G., Digilio, M., Sarkozy, A., Marino, B.,  
818 Dallapiccola, B., & Calabrò, R. (2006). Diffuse coronary dilation in a young patient with  
819 LEOPARD syndrome. *International Journal of Cardiology*, 112(2), e35-37.  
820 <https://doi.org/10.1016/j.ijcard.2006.02.037>
- 821 Pandit, B., Sarkozy, A., Pennacchio, L. A., Carta, C., Oishi, K., Martinelli, S., Pogna, E. A.,  
822 Schackwitz, W., Ustaszewska, A., Landstrom, A., Bos, J. M., Ommen, S. R., Esposito, G., Lepri,  
823 F., Faul, C., Mundel, P., López Sigüero, J. P., Tenconi, R., Selicorni, A., ... Gelb, B. D. (2007).  
824 Gain-of-function RAF1 mutations cause Noonan and LEOPARD syndromes with hypertrophic  
825 cardiomyopathy. *Nature Genetics*, 39(8), 1007–1012. <https://doi.org/10.1038/ng2073>
- 826 Pierpont, M. E., & Digilio, M. C. (2018). Cardiovascular disease in Noonan syndrome: *Current*  
827 *Opinion in Pediatrics*, 30(5), 601–608. <https://doi.org/10.1097/MOP.0000000000000669>
- 828 Pierpont, M. E. M., Magoulas, P. L., Adi, S., Kavamura, M. I., Neri, G., Noonan, J., Pierpont, E. I.,  
829 Reinker, K., Roberts, A. E., Shankar, S., Sullivan, J., Wolford, M., Conger, B., Santa Cruz, M., &  
830 Rauen, K. A. (2014). Cardio-facio-cutaneous syndrome: Clinical features, diagnosis, and  
831 management guidelines. *Pediatrics*, 134(4), e1149-1162. <https://doi.org/10.1542/peds.2013-3189>
- 832 Power, P. D., Lewin, M. B., Hannibal, M. C., & Glass, I. A. (2006). Aortic root dilatation is a rare  
833 complication of Noonan syndrome. *Pediatric Cardiology*, 27(4), 478–480.  
834 <https://doi.org/10.1007/s00246-006-1210-x>
- 835 Pradhan, A. K., Pandey, S., Usman, K., Kumar, M., & Mishra, R. (2013). Noonan syndrome with  
836 complete atrioventricular canal defect with pulmonary stenosis. *Journal of the American College of*  
837 *Cardiology*, 62(20), 1905. <https://doi.org/10.1016/j.jacc.2013.06.062>

- 1  
2  
3 838 Prendiville, T. W., Gauvreau, K., Tworog-Dube, E., Patkin, L., Kucherlapati, R. S., Roberts, A. E.,  
4 & Lacro, R. V. (2014). Cardiovascular disease in Noonan syndrome. *Archives of Disease in*  
5 839 *Childhood*, 99(7), 629–634. <https://doi.org/10.1136/archdischild-2013-305047>  
6 840  
7  
8  
9 841 Purnell, R., Williams, I., Von Oppell, U., & Wood, A. (2005). Giant aneurysms of the sinuses of  
10  
11 842 Valsalva and aortic regurgitation in a patient with Noonan's syndrome. *European Journal of*  
12  
13 843 *Cardio-Thoracic Surgery: Official Journal of the European Association for Cardio-Thoracic*  
14 844 *Surgery*, 28(2), 346–348. <https://doi.org/10.1016/j.ejcts.2005.05.004>  
15  
16  
17 845 Rapezzi, C., Arbustini, E., Caforio, A. L. P., Charron, P., Gimeno-Blanes, J., Heliö, T., Linhart, A.,  
18 846 Mogensen, J., Pinto, Y., Ristic, A., Seggewiss, H., Sinagra, G., Tavazzi, L., & Elliott, P. M. (2013).  
19  
20 847 Diagnostic work-up in cardiomyopathies: Bridging the gap between clinical phenotypes and final  
21  
22 848 diagnosis. A position statement from the ESC Working Group on Myocardial and Pericardial  
23  
24 849 Diseases. *European Heart Journal*, 34(19), 1448–1458. <https://doi.org/10.1093/eurheartj/ehs397>  
25  
26 850 Rauen, K. A. (2013). The RASopathies. *Annual Review of Genomics and Human Genetics*, 14,  
27  
28 851 355–369. <https://doi.org/10.1146/annurev-genom-091212-153523>  
29  
30 852 Razzaque, M. A., Nishizawa, T., Komoike, Y., Yagi, H., Furutani, M., Amo, R., Kamisago, M.,  
31  
32 853 Momma, K., Katayama, H., Nakagawa, M., Fujiwara, Y., Matsushima, M., Mizuno, K., Tokuyama,  
33  
34 854 M., Hirota, H., Muneuchi, J., Higashinakagawa, T., & Matsuoka, R. (2007). Germline gain-of-  
35 855 function mutations in RAF1 cause Noonan syndrome. *Nature Genetics*, 39(8), 1013–1017.  
36  
37 856 <https://doi.org/10.1038/ng2078>  
38  
39 857 Roberts, A. E., Allanson, J. E., Tartaglia, M., & Gelb, B. D. (2013). Noonan syndrome. *Lancet*  
40  
41 858 (*London, England*), 381(9863), 333–342. [https://doi.org/10.1016/S0140-6736\(12\)61023-X](https://doi.org/10.1016/S0140-6736(12)61023-X)  
42  
43 859 Roberts, A. E., Araki, T., Swanson, K. D., Montgomery, K. T., Schiripo, T. A., Joshi, V. A., Li, L.,  
44  
45 860 Yassin, Y., Tamburino, A. M., Neel, B. G., & Kucherlapati, R. S. (2007). Germline gain-of-  
46  
47 861 function mutations in SOS1 cause Noonan syndrome. *Nature Genetics*, 39(1), 70–74.  
48  
49 862 <https://doi.org/10.1038/ng1926>  
50  
51 863 Rodriguez-Viciana, P., Tetsu, O., Tidyman, W. E., Estep, A. L., Conger, B. A., Cruz, M. S.,  
52  
53 864 McCormick, F., & Rauen, K. A. (2006). Germline mutations in genes within the MAPK pathway  
54 865 cause cardio-facio-cutaneous syndrome. *Science (New York, N.Y.)*, 311(5765), 1287–1290.  
55  
56 866 <https://doi.org/10.1126/science.1124642>  
57  
58  
59 867 Romano, A. A., Allanson, J. E., Dahlgren, J., Gelb, B. D., Hall, B., Pierpont, M. E., Roberts, A. E.,  
60 868 Robinson, W., Takemoto, C. M., & Noonan, J. A. (2010). Noonan syndrome: Clinical features,

1  
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58  
59  
60

- diagnosis, and management guidelines. *Pediatrics*, 126(4), 746–759.  
<https://doi.org/10.1542/peds.2009-3207>
- Ruiz-Llobet, A., Isola, I., Gassiot, S., Català, A., Díaz-Ricart, M., Martínez-Monseny, A. F., Serrano, M., & Berrueco, R. (2020). Platelet Dysfunction in Noonan and 22q11.2 Deletion Syndromes in Childhood. *Thrombosis and haemostasis*, 120(3), 457–465. <https://doi.org/10.1055/s-0040-1701239>
- Sarkozy, A., Conti, E., Seripa, D., Digilio, M. C., Grifone, N., Tandoi, C., Fazio, V. M., Di Ciommo, V., Marino, B., Pizzuti, A., & Dallapiccola, B. (2003). Correlation between PTPN11 gene mutations and congenital heart defects in Noonan and LEOPARD syndromes. *Journal of Medical Genetics*, 40(9), 704–708. <https://doi.org/10.1136/jmg.40.9.704>
- Sarkozy, A., Digilio, M. C., & Dallapiccola, B. (2008). Leopard syndrome. *Orphanet Journal of Rare Diseases*, 3, 13. <https://doi.org/10.1186/1750-1172-3-13>
- Scott, A., Giosaffatte, N. D., Pinna, V., Daniele, P., Corno, S., D’Ambrosio, V., Andreucci, E., Marozza, A., Sirchia, F., Tortora, G., Mangiameli, D., Marco, C. D., Romagnoli, M., Donati, I., Zonta, A., Grosso, E., Naretto, V. G., Mastromoro, G., Versacci, P., ... Luca, A. D. (2021). When to test fetuses for RASopathies? Proposition from a systematic analysis of 352 multicenter cases and a postnatal cohort. *Genetics in Medicine*, 23(6), 1116–1124. <https://doi.org/10.1038/s41436-020-01093-7>
- Shachter, N., Perloff, J. K., & Mulder, D. G. (1984). Aortic dissection in Noonan’s syndrome (46 XY turner). *The American Journal of Cardiology*, 54(3), 464–465. [https://doi.org/10.1016/0002-9149\(84\)90228-5](https://doi.org/10.1016/0002-9149(84)90228-5)
- Shaw, A. C., Kalidas, K., Crosby, A. H., Jeffery, S., & Patton, M. A. (2007). The natural history of Noonan syndrome: A long-term follow-up study. *Archives of Disease in Childhood*, 92(2), 128–132. <https://doi.org/10.1136/adc.2006.104547>
- Smpokou, P., Tworog-Dube, E., Kucherlapati, R. S., & Roberts, A. E. (2012). Medical complications, clinical findings, and educational outcomes in adults with Noonan syndrome. *American Journal of Medical Genetics. Part A*, 158A(12), 3106–3111. <https://doi.org/10.1002/ajmg.a.35639>
- Stout, K. K., Daniels, C. J., Aboulhosn, J. A., Bozkurt, B., Broberg, C. S., Colman, J. M., Crumb, S. R., Dearani, J. A., Fuller, S., Gurvitz, M., Khairy, P., Landzberg, M. J., Saidi, A., Valente, A. M., & Van Hare, G. F. (2019). 2018 AHA/ACC Guideline for the Management of Adults With Congenital

1

2

3 900 [Heart Disease: A Report of the American College of Cardiology/American Heart Association Task](#)

4 901 [Force on Clinical Practice Guidelines. \*Circulation\*, 139\(14\), e698–e800.](#)

5 902 <https://doi.org/10.1161/CIR.0000000000000603>

6

7 903 Tartaglia, M., & Gelb, B. D. (2010). Disorders of dysregulated signal traffic through the RAS-  
8 904 MAPK pathway: Phenotypic spectrum and molecular mechanisms. *Annals of the New York*  
9 905 *Academy of Sciences*, 1214, 99–121. <https://doi.org/10.1111/j.1749-6632.2010.05790.x>

10

11 906 Tartaglia, M., Kalidas, K., Shaw, A., Song, X., Musat, D. L., van der Burgt, I., Brunner, H. G.,  
12 907 Bertola, D. R., Crosby, A., Ion, A., Kucherlapati, R. S., Jeffery, S., Patton, M. A., & Gelb, B. D.  
13 908 (2002). PTPN11 Mutations in Noonan Syndrome: Molecular Spectrum, Genotype-Phenotype  
14 909 Correlation, and Phenotypic Heterogeneity. *The American Journal of Human Genetics*, 70(6),  
15 910 1555–1563. <https://doi.org/10.1086/340847>

16

17 911 Tartaglia, M., Mehler, E. L., Goldberg, R., Zampino, G., Brunner, H. G., Kremer, H., van der Burgt,  
18 912 I., Crosby, A. H., Ion, A., Jeffery, S., Kalidas, K., Patton, M. A., Kucherlapati, R. S., & Gelb, B. D.  
19 913 (2001). Mutations in PTPN11, encoding the protein tyrosine phosphatase SHP-2, cause Noonan  
20 914 syndrome. *Nature Genetics*, 29(4), 465–468. <https://doi.org/10.1038/ng772>

21

22 915 Tartaglia, M., Pennacchio, L. A., Zhao, C., Yadav, K. K., Fodale, V., Sarkozy, A., Pandit, B., Oishi,  
23 916 K., Martinelli, S., Schackwitz, W., Ustaszewska, A., Martin, J., Bristow, J., Carta, C., Lepri, F.,  
24 917 Neri, C., Vasta, I., Gibson, K., Curry, C. J., ... Gelb, B. D. (2007). Gain-of-function SOS1  
25 918 mutations cause a distinctive form of Noonan syndrome. *Nature Genetics*, 39(1), 75–79.  
26 919 <https://doi.org/10.1038/ng1939>

27

28 920 Umeki, I., Niihori, T., Abe, T., Kanno, S., Okamoto, N., Mizuno, S., Kurosawa, K., Nagasaki, K.,  
29 921 Yoshida, M., Ohashi, H., Inoue, S., Matsubara, Y., Fujiwara, I., Kure, S., & Aoki, Y. (2019).  
30 922 Delineation of LZTR1 mutation-positive patients with Noonan syndrome and identification of  
31 923 LZTR1 binding to RAF1–PPP1CB complexes. *Human Genetics*, 138(1), 21–35.  
32 924 <https://doi.org/10.1007/s00439-018-1951-7>

33

34 925 [Wehrens, X. H., Lehnart, S. E., Reiken, S. R., Deng, S. X., Vest, J. A., Cervantes, D., Coromilas, J.,](#)  
35 926 [Landry, D. W., & Marks, A. R. \(2004\). Protection from cardiac arrhythmia through ryanodine](#)  
36 927 [receptor-stabilizing protein calstabin2. \*Science \(New York, N.Y.\)\*, 304\(5668\), 292–296.](#)  
37 928 <https://doi.org/10.1126/science.1094301>

38

39 929 Wolf, C. M., Zenker, M., Burkitt-Wright, E., Edouard, T., García-Miñaur, S., Lebl, J., Shaikh, G.,  
40 930 Tartaglia, M., Verloes, A., & Östman-Smith, I. (2022). Management of cardiac aspects in children

1  
2  
3 931 with Noonan syndrome—Results from a European clinical practice survey among paediatric  
4 932 cardiologists. *European Journal of Medical Genetics*, 65(1), 104372.  
5 933 <https://doi.org/10.1016/j.ejmg.2021.104372>  
6  
7  
8  
9 934 Yamamoto, G. L., Agüena, M., Gos, M., Hung, C., Pilch, J., Fahiminiya, S., Abramowicz, A.,  
10 935 Cristian, I., Buscarilli, M., Naslavsky, M. S., Malaquias, A. C., Zatz, M., Bodamer, O., Majewski,  
11 936 J., Jorge, A. A. L., Pereira, A. C., Kim, C. A., Passos-Bueno, M. R., & Bertola, D. R. (2015). Rare  
12 937 variants in *SOS2* and *LZTR1* are associated with Noonan syndrome. *Journal of Medical Genetics*,  
13 938 52(6), 413–421. <https://doi.org/10.1136/jmedgenet-2015-103018>  
14  
15  
16  
17  
18 939 Yaoita, M., Niihori, T., Mizuno, S., Okamoto, N., Hayashi, S., Watanabe, A., Yokozawa, M.,  
19 940 Suzumura, H., Nakahara, A., Nakano, Y., Hokosaki, T., Ohmori, A., Sawada, H., Migita, O., Mima,  
20 941 A., Lapunzina, P., Santos-Simarro, F., García-Miñaur, S., Ogata, T., ... Aoki, Y. (2016). Spectrum  
21 942 of mutations and genotype–phenotype analysis in Noonan syndrome patients with RIT1 mutations.  
22 943 *Human Genetics*, 135(2), 209–222. <https://doi.org/10.1007/s00439-015-1627-5>  
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## 32 946 **FIGURE LEGENDS**

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34 947 **Figure 1.** Diagnosis–treatment flow-chart for congenital heart defects associated with  
35 948 RASopathies.

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37 949 Abbreviations: CHDs, congenital heart defects; PVS, pulmonary valve stenosis; ASD, atrial  
38 950 septal defect; AVSD, atrioventricular septal defect; VSD, ventricular septal defect; PDA, patent  
39 951 ductus arteriosus; MV, mitral valve; ECG, electrocardiogram.

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41 952 **Figure 2.** Diagnostic flow-chart for hypertrophic cardiomyopathy associated with  
42 953 RASopathies.

43 954 Abbreviations: ASD, atrial septal defect; AVSD, atrioventricular septal defect; CHDs,  
44 955 congenital heart defects; CS, Costello syndrome; MV, mitral valve; NGS, next-generation  
45 956 sequencing; NSML, Noonan syndrome with multiple lentigines; PVS, pulmonary valve stenosis;  
46 957 VSD, ventricular septal defect.

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48 958 **Figure 3.** Determinants and management of left ventricular outflow tract obstruction in  
49 959 hypertrophic cardiomyopathy associated with RASopathies.  
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**Congenital Heart Defects**

**Common CHDs**  
  
PVS  
ASD  
AVSD

**Less common CHDs**  
  
VSD, PDA  
MV dysplasia  
Left-sided obstructive CHDs  
Coronary artery anomalies  
Others

Clinical examination  
Echocardiography, ECG, chest X-ray,  
24-h ECG Holter monitoring

Symptoms related to CHDs  
Significant hemodynamic lesion  
Arrhythmias

**Intervention depending on CHDs:  
percutaneous or surgical repair**

**Medical treatment**

**Regular follow-up  
Imaging**

**Treat medical comorbidities**

**YES**

**NO**



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CHDs: PVS, MV dysplasia, ASD, VSD, AVSD, coronary artery abnormalities  
 Extreme right axis deviation  
 Prolonged QT (NSML)  
 Atrial tachyarrhythmias (CS)

Hypertrophic cardiomyopathy

Facial dysmorphisms  
 Dermatological abnormalities (e.g., lentigines, café-au-lait spots)  
 Cryptorchidism  
 Sensorineural deafness  
 Short stature

Systematic screening for cardiac or extracardiac red flags for RASopathies

Genetic analysis  
 (NGS panel including known genes associated with RASopathies)

Pathogenic variant

Variant of uncertain significance

Negative or benign variant

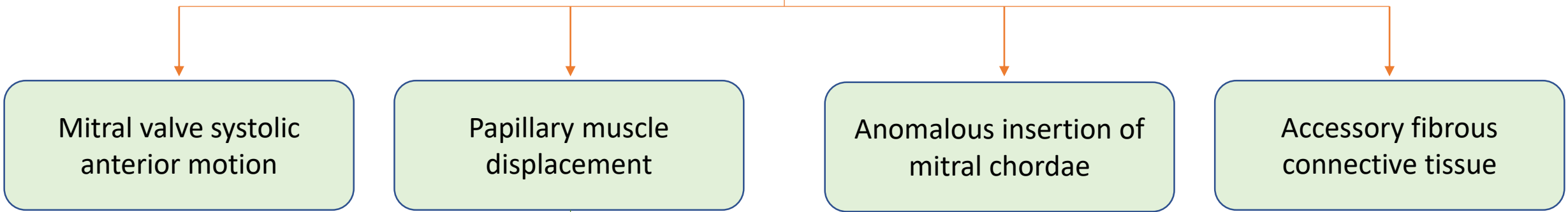
Diagnosis of RASopathy

Assessment of variant pathogenicity

Diagnosis of RASopathy unlikely

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Left ventricular outflow tract obstruction



Left ventricular outflow tract gradient  $\geq 50$  mmHg

