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RECOMMENDATIONS AND GUIDELINES

# Clinical management, ethics and informed consent related to multi-gene panel-based high throughput sequencing testing for platelet disorders: Communication from the SSC of the ISTH

Kate Downes[1,2] | Pascal Borry[3] | Katrin Ericson[4] | Keith Gomez[5] | Andreas Greinacher[6] | Michele Lambert[7,8] | Eva Leinoe[9] | Patrizia Noris[10] | Chris Van Geet[11] | Kathleen Freson[11] |

Subcommittee on Genomics in Thrombosis, Hemostasis

[1]East Genomic Laboratory Hub, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

[2]Department of Haematology, University of Cambridge, Cambridge Biomedical Campus, Cambridge, UK

[3]Department of Public Health and Primary Care, KU Leuven, Leuven, Belgium

[4]The RUNX1 Research Program, Santa Barbara, CA, USA

[5]Haemophilia Centre and Thrombosis Unit, Royal Free London NHS Foundation Trust, London, UK

[6]Institut für Immunologie und Transfusionsmedizin, Universitätsmedizin Greifswald, Greifswald, Germany

[7]Division of Hematology, The Children's Hospital of Philadelphia, Philadelphia, PA, USA

[8]Department of Pediatrics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

[9]Department of Haematology, Rigshospitalet, National University Hospital, Copenhagen, Denmark

[10]IRCCS Policlinico San Matteo Foundation and University of Pavia, Pavia, Italy

[11]Department of Cardiovascular Sciences, Center or Molecular and Vascular Biology, KU Leuven, Leuven, Belgium

**Correspondence**
Kathleen Freson, Center for Molecular and Vascular Biology, Herestraat 49 Bus 911, 3000 Leuven, Belgium.
Email: Kathleen.freson@kuleuven.be

## Abstract

Molecular diagnostics of inherited platelet disorders (IPD) has been revolutionized by the implementation of high-throughput sequencing (HTS) approaches. A conclusive diagnosis using HTS tests can be obtained quickly and cost-effectively in many, but not all patients. The expanding use of HTS tests has raised concerns regarding complex variant interpretation and the ethical implications of detecting unsolicited findings such as variants in IPD genes *RUNX1*, *ETV6*, and *ANKRD26*, which are associated with increased leukemic risk. This guidance document has been developed and written by a multidisciplinary team of researchers and clinicians, with expertise in hematology, clinical and molecular genetics, and bioethics, alongside a *RUNX1* patient advocacy representative. We recommend that for clinical diagnostics, HTS for IPD should use a multigene panel of curated diagnostic-grade genes. Critically, we advise that an HTS test for clinical diagnostics should only be ordered by a clinical expert that is: (a) fully aware of the

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complexity of genotype-phenotype correlations for IPD; (b) able to discuss these complexities with a patient and family members before the test is initiated; and (c) able to interpret and appropriately communicate the results of a HTS diagnostic report, including the implication of variants of uncertain clinical significance. Each patient should know what an HTS test could mean for his or her clinical management before initiating a test. We hereby propose an exemplified informed consent document that includes information on these ethical concerns and can be used by the community for implementation of HTS of IPD in a clinical diagnostic setting. This paper does not include recommendations for HTS of IPD in a research setting.

**KEYWORDS**

blood platelet disorders, consent forms, ethics, high-throughput nucleotide sequencing

## 1 | INTRODUCTION TO INHERITED PLATELET DISORDERS

Inherited platelet disorders (IPD) are caused by germline genetic variation in genes involved in the function and/or formation of platelets from megakaryocytes. IPD are extremely heterogeneous, with more than 60 genes now known to be associated with these disorders.[1] These genes can be classified according to their predicted role in platelet formation and function[2,3] (Table S1). IPD typically result in mild to severe bleeding symptoms, spontaneous or related to hemostatic challenges including trauma, surgery, pregnancy, and delivery. Bleeding is mucocutaneous and symptoms include petechiae, ecchymoses, epistaxis, menorrhagia, and gastrointestinal hemorrhage.[4] However, some IPD are not associated with obvious bleeding symptoms and patients with inherited thrombocytopenias may be identified incidentally during routine investigations that include a complete full blood count. Table S1 summarizes the main platelet phenotypes associated with pathogenic variants in genes that cause IPD. Deleterious variants in genes that are expressed in other blood cell types or tissues are often associated with broader clinical phenotypes.

**Glossary**

*Virtual gene panel*: Predefined panel of disease-causing genes that are selected from whole exome or whole genome sequencing datafiles for the analysis and reporting of variants.

*Unsolicited findings*: Variants in disease-causing genes that are unrelated to the original rationale for testing and that are identified inadvertently (eg, RUNX1, ETV6, and ANKRD26 variants that are risk factors for leukemia when testing for inherited thrombocytopenia or carriership of variants in recessive genes).

*Secondary findings*: Variants in disease-causing genes that are unrelated to the original rationale for testing but should be actively sought during the analysis. This refers to the medically actionable gene list from the American College of Medical Genetics and Genomics for conditions as hereditary cancer and cardiac diseases.

## 2 | DIAGNOSTICS OF IPD USING PANEL-BASED HIGH-THROUGHPUT SEQUENCING

As in other rare inherited diseases, several high-throughput sequencing (HTS) approaches have recently been introduced into research and clinical diagnostic laboratories that study IPD. HTS technologies have transformed the field of IPD with the discovery of more than 20 genes (Table S1) using whole exome and whole genome sequencing since 2011.[2,5] Clinical testing of candidate genes by Sanger sequencing and linkage analysis have now largely been replaced by sequencing techniques, mostly using targeted gene panel tests or whole exome sequencing, to survey multiple genes simultaneously. These tests are routinely used in many countries.[6] To improve HTS testing in a clinical setting, the International Society on Thrombosis and Haemostasis (ISTH) Scientific and Standardization Committee for Genetics in Thrombosis and Hemostasis has recently curated the "diagnostic-grade genes" (Table S1) associated with bleeding, thrombotic, and platelet disorders, which is updated annually.[1] Most guidelines recommend the use of such disease-specific multigene targeted or virtual panels in diagnostic HTS to prevent the detection of unsolicited findings (variants identified in disease-causing genes unrelated to the original rationale for testing) or the detection of variants in genes without sufficient genotype-phenotype evidence of a pathological phenotype in humans.[7]

Usually, several candidate disease-causing DNA variants are identified when using HTS technology to survey multiple genes. Correct pathogenicity scoring of these variants is crucial for diagnosis and counseling. A molecular diagnostic service should therefore have an array of available expertise, including a multidisciplinary team comprising of clinicians, geneticists, nonclinical platelet

experts, and bioinformaticians.[8] Together they can generate an integrated report with recommendations that are comprehensible for clinicians to allow for appropriate communication of results back to patients. Guidelines for variant classification have been formulated by the American College of Medical Genetics.[9] Pathogenic and likely pathogenic variants are reported in clinical genetic reports to inform clinicians and patients that these are disease-causing. However, for some variants, there is not enough evidence available at the time of interpretation to define these as likely pathogenic or likely benign. These are variants of uncertain significance (VUS) that alone should not be used to inform clinical practice.[10]

To date, current practices regarding the inclusion, or exclusion, of VUS in a diagnostic genetic report vary.[11] A clinician receiving a report containing VUS could use this information to order further functional tests and family studies that could inform on the pathogenicity of the variant. Because VUS will have to be discussed with the patient, it is essential to provide a clear explanation of VUS, and the possibility for a change of the initial genetic report in the future. Therefore, to avoid misinterpretation of VUS findings and provide appropriate counseling, it is strongly advised that an HTS test for clinical diagnostics and inclusion of VUS reporting should only be requested by clinicians experienced in genetic interpretation. Laboratory reports should clearly distinguish between VUS and (likely) pathogenic variants to reduce potential confusion. Reporting VUS and initiating further studies is an extension of standard patient care. It is of crucial importance when considering VUS that data sharing is promoted to allow for improved interpretation of variants. We endorse that reported variants should be routinely shared in variant databases provided the patient is deidentified, appropriate data protection mechanisms are in place, and patients are notified their data will be shared.

What diagnostic rate can we expect when performing a multigene panel HTS test for IPD? A recent review compared the diagnostic rate obtained in different HTS studies for IPD and the main conclusion is that this strongly depends on the patient inclusion criteria.[6] Thrombogenomics, the largest HTS study performed to date, shows that when performing an HTS test on DNA from 335 patients with suspected inherited (macro)thrombocytopenia and 430 patients with a known platelet function disorder confirmed by laboratory tests, a diagnostic rate of 47.8% and 26.1% was obtained, respectively.[12] The low diagnostic rate for the platelet function disorders in this study was due to the inclusion of patients with isolated delta storage pool disease for which the gene(s) are still unknown. If a patient's exome or genome sequence has been used for diagnostics, and no pathogenic variants identified, the data can be used for gene discovery in a research setting.

## 3 | HOW GENETIC TEST RESULTS INFORM CLINICAL MANAGEMENT OF IPD

As with many rare diseases, a genetic test result for IPD may help health professionals provide information to patients regarding disease prognosis and management, as well as family planning and counseling, and in some cases even disease prevention approaches. In addition, patients with a genetic condition may also just "want to know" why their symptoms occur.

Therapeutic options for the management of bleeding symptoms present in most IPD are limited and include the administration of desmopressin, platelet transfusions, recombinant FVIIa, and antifibrinolytics.[4] The result of a genetic test currently does not have much influence on the bleeding management strategy. However, for some IPD, the type of variant can predict bleeding severity. For example, Glanzmann thrombasthenia patients with a null variant generally have more severe bleeding problems compared to those with missense variants, and they are at higher risk of developing isoantibodies when transfused with platelets and should therefore preferentially be treated with rFVIIa. Another example is the difference in treatment for platelet-type von Willebrand disease and von Willebrand disease type 2B. Patients with platelet-type von Willebrand disease are treated with platelet transfusions, whereas von Willebrand disease type 2B patients are treated with von Willebrand factor concentrates.[20] Both conditions share similar platelet phenotypes including enhanced binding between von Willebrand factor and glycoprotein (GP) Ib alpha, and thrombocytopenia.[13] Although functional assays can help differentiate between these disorders,[13,14] the differential diagnosis relies largely on genetic studies.[14]

An HTS gene panel test designed using the ISTH-curated genes[1] contains more than 35 genes known to cause thrombocytopenia. Genetic variants in these genes have also been identified in patients with low platelet counts that were initially treated for immune thrombocytopenia.[12] Therefore, if thrombocytopenia is detected in a patient with a positive family history, a gene panel test may be useful to provide a correct diagnosis and prevent unnecessary and potentially harmful treatments such as a splenectomy. Some thrombocytopenia genes are also known risk factors for leukemia.[15,16] Germline genetic defects in *RUNX1*, *ETV6*, and *ANKRD26* can predispose to hematologic malignancies with an estimated lifetime risk of about 45%, 30%, and 4.9%, respectively.[17] *WAS* variants are associated with increased risk of lymphoma, lymphoblastic leukemia, myelodysplasia, and myeloproliferative disorders with a prevalence of approximately 13%.[18] An accurate molecular diagnosis of patients with these genetic defects can improve our understanding of these diseases and may improve cancer risk predictions, which will ultimately benefit patients and their families in future generations. Today, the knowledge of these genetic predispositions to malignancy informs clinicians of the need to perform regular hematological evaluations and to provide family counseling. If allogenic bone marrow transplantation is required in a leukemic patient who has a germline risk variant, a genetic test in any potential donor family members is highly recommended because some affected individuals may be asymptomatic with borderline normal platelet counts. Moreover, if genetic studies for these genes have never been undertaken, there is a risk that a leukemic patient will receive stem cells from an affected family donor with a variant in such gene. A molecular diagnosis in some other thrombocytopenia genes can also provide prognostic information for the development of specific symptoms

with age. For patients with macrothrombocytopenia, a pathogenic variant in *MYH9* or *DIAPH1* can result in hearing loss and, for *MYH9*, also in kidney failure.[19,20] For *MYH9*, avoidance of nephrotoxic medications can reduce the risk of progression to renal failure. Some initial genotype-phenotype relations are known for MYH9 and it is accepted that some *MYH9* variants do result in more severe phenotypes than others.[19] For specific inherited thrombocytopenias with defects in *MYH9*, *WAS*, *ANKRD26*, *DIAPH1*, and monoallelic *GP1BA/GP1BB*, a patient's platelet count can be raised by supplying THPO-receptor agonists, such as eltrombopag and romiplostim.[21-23] Variants in *FERMT3*, *WAS*, *MECOM*, and *MPL* can result in severe immune disease, pancytopenia, or bone marrow failure that often requires bone marrow transplantation.[24-26] Early initiation of donor search and stem cell transplantation can prevent immunization by repeated transfusions because of progressive bone marrow failure. In contrast, thrombocytopenia with bone marrow failure from biallelic *THPO* variants does not respond to bone marrow transplantation and is treatable with romiplostim.[27] Finally, *KDSR*-related thrombocytopenia appears to improve with age.[28] An HTS test can provide similar important prognostic information for patients with Hermansky Pudlak syndrome (HPS). Ten different genes cause HPS that include a variable degree of bleeding, delta storage pool disease, and oculocutaneous albinism, but only *HPS1*, *HPS4*, and *AP3B1* defects can cause pulmonary fibrosis,[29,30] *HPS1* and *HPS4* defect can also cause kidney disease and colitis [31] and only pathogenic variants in *AP3B1* and *AP3D1* are associated with immune disease.[30,32]

## 4 | LIMITATIONS AND ETHICAL ISSUES RELATED TO DIAGNOSTIC HTS GENE PANEL TESTING FOR IPD

Although HTS panel tests for IPD can result in rapid and cost-effective diagnoses, such tests also have limitations, and have recently raised ethical concerns.[15,16] Panel tests for IPD are currently available in clinical diagnostic labs but also from private companies with costs that are highly variable. The turn-around time mostly varies between 3-4 months. Table S2 and the Appendix S1 provide an overview of strengths and weaknesses of the classical approach vs HTS for the genetic diagnosis of IPD.

The main point of concern are the ethical issues that can occur with HTS of IPD. If for example pathogenic variants are detected in either *RUNX1*, *ETV6* or *ANKRD26* in a patient with thrombocytopenia or platelet dysfunction without a family history of leukemia, such variants can be considered as an unsolicited finding if the patient was not aware about these genetic risk factors for leukemia before initiating the HTS test.[15,16] Various documents have recommended that the informed consent process should ensure that patients comprehend the possible detection risk of unsolicited findings. Patients should be asked before testing whether they want to receive unsolicited findings and they should be able to opt-out. The informed consent process should explain the likelihood of unsolicited findings and the reporting approach taken.[33] In addition, it is possible to detect a carrier status of recessive genes.[12] It is generally advised that if carrier status is identified, regardless of whether it relates to the clinical question, it should be reported if informed consent is obtained prior to testing. This is because knowing one's carrier status can increase reproductive options.[34]

An additional important ethical issue to be considered is when it is appropriate for children to be tested. Clinical guidelines have emphasized the importance of not testing children, unless there is a clear medical benefit for the minor.[35] In the context of diagnosis, a confirmative molecular diagnosis is a major advantage. In other situations, deferring testing might allow minors to make personal decisions about testing later in life, hereby respecting their right not to know. For this reason, predictive genetic testing, which has little impact on the clinical management of the platelet disorder is not recommended and should be deferred until the minor is able to consent for themselves. Currently, the information of pathogenic variants in *RUNX1*, *ANKRD26* or *ETV6* cannot inform prevention of hematologic malignancies but it can suggest leukemic surveillance protocols and ultimately impact treatment at the time of cancer diagnosis. Knowledge of these germline genetic disorders also informs careful selection of a non-affected family member as a stem cell donor for allogeneic bone marrow transplantation. Some parents, and potentially older minors, may feel relieved by leukemic surveillance, which would not be routine practice if the genetic variant was not known. To conclude, as HTS testing for IPD clearly involves ethical concerns related to unsolicited findings, it should be mandatory that patients (and parents) are informed prior to initiating testing.[36]

Secondary findings comprise results that are not the primary target of the test but rather an additional result actively sought by the clinician. When applying a multi-gene panel HTS test for IPD, the detection of secondary findings is avoided.

## 5 | IMPLEMENTATION OF INFORMED CONSENT WHEN APPLYING DIAGNOSTIC HTS TESTING FOR IPD

It is important that a patient/parent understands the testing procedure, the benefits and limitations of the test, and the possible consequences of the test results in relation to clinical management options. Advice on how the informed consent can improve the communication between the patient, clinician, and the HTS laboratory and what information should be included has been suggested by multiple studies.[37,38] Such formal written informed consent is not always taken for a diagnostic multigene panel HTS tests, but is strongly recommended in most countries and is in fact mandatory in others. Such an informed consent could be used by clinicians to direct a conversation with patients to prevent problems with unsolicited findings and other ethical issues.

In this guidance document, we suggest a general consent that is easy to understand for all patients, clearly mentions the test expectations in relation to their clinical management, and points to the possibility of unsolicited findings. Table 1 proposes information that

**TABLE 1** Guidance for discussion and recommended text to be included in an informed consent for HTS of IPD

| Recommended items to include in the informed consent of diagnostic panel-based HTS test for IPD | Example of text for informed consent for patients (in between brackets is adjusted informed consent for parents) |
|---|---|
| Information:<br>What is an HTS test for IPD? | You (or your child) is suspected of having an IPD based on clinical and/or laboratory evidence and/or family history. This might include platelet dysfunction or an abnormal low platelet count (thrombocytopenia) associated with bleeding or other clinical symptoms. These symptoms may be caused by a change in the DNA of a specific gene, called a variant, that may have been passed down from generation to generation or occurs for the first time as a novel variant (de novo). A confirmative genetic diagnosis of this IPD can sometimes be obtained using an HTS test. The test is a DNA-based analysis of all genes that are currently known to cause an IPD. |
| Information:<br>What are the limitations of an HTS test? | Some IPD cannot be explained by a genetic diagnosis because the gene defects for these disorders are not yet known or the genetic change may be missed because of technical limitations of the test. Sometimes a genetic change is found, but it is not clear whether it is the cause of an IPD or not. These are known as "variants of uncertain significance" (VUS). |
| Information:<br>What type of genetic report will I receive? | You (or your child) can receive three types of genetic reports when HTS test is performed: (a) a disease-causing, referred to as pathogenic, DNA variant is found that can explain your IPD (the IPD in your child); (b) no DNA variant is found that can explain your IPD (the IPD in your child); and (c) a DNA variant is found that requires further studies because its clinical significance is not clear. This type of variant is sometimes referred to as a VUS |
| Information:<br>Implication for family members | The results of a genetic test for IPD are likely to have implications for your (your child's) family members. It is encouraged to discuss that you (your child) are being tested for an IPD with your (your child's) family. Your (your child's) family members can be informed about the option for genetic counselling.<br>You may be asked to share your (your child's) genetic test report with the clinician of family members. |
| Information:<br>Are there any risks involved? | A genetic change may be identified that indicates a disorder, or the risk of having or carrying a disorder, that is not part of the IPD that you (your child) is being tested for.<br>There may be unexpected findings. For example, the results might indicate that the relationship between family members is not what is expected. |
| Patient choice:<br>Opt_in/Opt_out choice for testing of IPD genes that are also associated with an increased risk of leukemia | The HTS test includes three genes (*RUNX1*, *ETV6*, and *ANKRD26*) that if a pathogenic variant is discovered, it is associated with an increased risk of leukemia, in addition to causing my IPD (the IPD in my child). The estimated risk for leukemia differs between these three genes. Close to one-half of patients (~44%) with a variant in *RUNX1* develop a blood cancer. The average age of onset is 33 y and approximately 25% who are diagnosed with a blood cancer are children. About one in three patients with *ETV6* variants develop leukemia. Among those who develop leukemia, most are children. About one in 20 patients with an *ANKRD26* variant develop leukemia. Among those who develop leukemia, most are adults.<br>Knowing the genetic variant will not help my clinician (the clinician of my child) predict my (his/her) precise risk for developing leukemia but the clinician can regularly test my (his/her) blood cell count and look for changes in my (his/her) bone marrow more closely. It is possible that close surveillance could help detect a blood cancer early and knowing the genetic variant would impact donor selection for bone marrow transplant.<br>I understand that a genetic test cannot prevent leukemia.<br>I understand that I have the "right not to know" about these unsolicited findings.<br>I have chosen (for my child) to analyze these three genes:<br>(YES) or (NO). |
| Patient choice:<br>Participation to the HTS test is voluntary | I understand that my participation (the participation of my child) to the HTS test for IPD is voluntary and that I am free to withdraw this participation (the participation of my child) at any time, without giving any reason and this will not alter the clinical care I (my child) receive. In this case, any further addition of data to my record (the record of my child) will be stopped. |
| Patient choice:<br>Sharing variants with other health care specialists to improve disease knowledge | My anonymized genetic variants (or genetic variants of my child) can be shared among health care professionals and laboratory scientists nationally or internationally in publicly accessible databases. This is done to compare the findings from patients with similar symptoms or variants, which can help to determine which variants may or may not be linked to a particular condition. Sharing data can also support ongoing research aimed at understanding how genetic variants cause disease and may potentially support the discovery of new treatments for a specific inherited condition. My privacy and my health status (The privacy and the health status of my child) is fully respected upon sharing the genetic information. No personal data are shared among other health care professionals or scientists. All data will be anonymized. |
| Patient choice:<br>Acknowledgment of expectations related to an HTS test for IPD | I want to know the genetic cause of my IPD (of the IPD present in my child). I have been told and understand how information about the genetic cause of my IPD may or may not change my clinical care (the clinical care of my child). I have been informed about the option for genetic counseling. |

(Continues)

**TABLE 1** (Continued)

| Recommended items to include in the informed consent of diagnostic panel-based HTS test for IPD | Example of text for informed consent for patients (in between brackets is adjusted informed consent for parents) |
|---|---|
| Additional items that can be included | |
| Patient choice: Opt_in/Opt_out choice for further studies of a VUS (type 3 report) | If my report (the report of my child) contains a DNA variant(s) that requires further studies and from which the relevance for my (their) IPD is not clear, I grant permission for my clinician to recontact me (on behalf of my child) for further studies: (YES) or (NO) |
| Patient choice: Opt_in/Opt_out choice for information regarding carriership of recessive conditions and implications | I would like to receive details of DNA variants that I carry (that my child carries). These DNA variants are not always directly related to my clinical condition (the clinical condition of my child). I want to know if I (my child) carry (carries) a DNA variant for a recessive disease: (YES) or (NO) |

is strongly recommended to be included in an informed consent for diagnostic HTS screening. Also, a specific informed consent example is provided that can be used for patients or the parent of a patient (Table 1). In addition, questions suggested in Table S3 can be used by patients during the process of consenting and by clinicians to test if their patients understands the consent.

## 6 | CONCLUDING RECOMMENDATIONS FOR LABORATORIES AND CLINICIANS

The implementation of HTS approaches to diagnose IPD has changed the field. With this communication, we provide information and also points of consideration for laboratories and clinicians who develop and use HTS tests for IPD in a diagnostic setting (Figure 1). We however do not provide recommendations for genetic studies in a research setting that are mainly focused on gene discovery and are outside the scope of this paper.

We recommend that laboratories use a multigene panel test that only involves curated diagnostic-grade genes that have a proven association with IPD.[1] Variant interpretation should follow American College of Medical Genetics criteria and are typically discussed during multidisciplinary meetings. Genetic reports include a clear distinction between pathogenic variants versus VUS. An information sheet can explain the expectations (inclusion criteria, mean diagnostic rates, turn-around time, cost, and more) and shortcomings (technical limitations, VUS detection, and more) of an HTS test for IPD. It is highly recommended to use a consent form for patient referral.

We also provide some recommendations for clinicians. Genetic testing for a heterogeneous condition such as IPD and understanding the impact is not straightforward; clinicians should

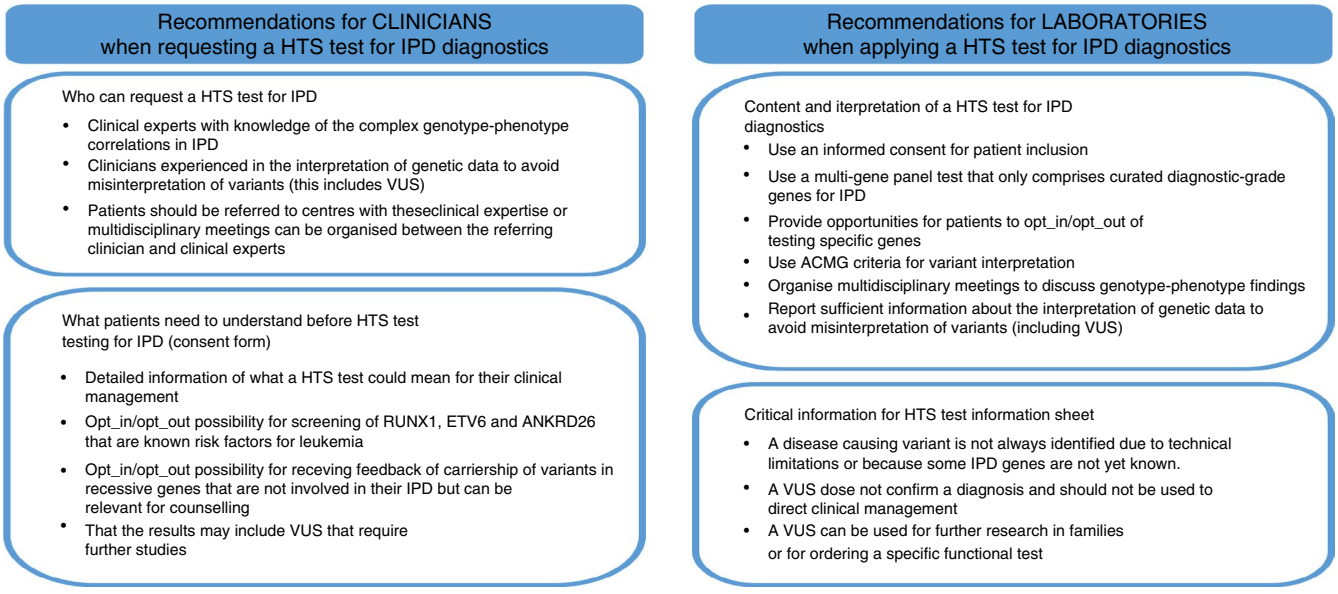


**FIGURE 1** Recommendation when applying a multigene panel test for IPD diagnostics for clinicians and laboratories

consider referring their patients to expert centers that perform HTS instead of sending patient samples to external laboratories.[39] Alternatively, multidisciplinary meetings can be organized between expert(s) and prescriber, to discuss a patient's suitability for testing, results interpretation and patient and family care. Such approaches can also promote the examination and reclassification of VUS. Screening all genes in a single assay, as is done with a multigene HTS approach, allows for a diagnosis of the "unexpected." However, this also involves the potential detection of unsolicited findings, including variants in genes associated with leukemic risk. Such variants typically present in families with autosomal dominant thrombocytopenia or bleeding, and a history of hematological malignancy. We recommend that patients should be well informed about this possibility before performing the test, preferably by using an informed consent document to aid discussion and provide a written record. This is in line with ethical debates related to how personalized medicine is creating a more patient-centered approach to health care,[40] highlighting the need for sufficient information and understanding to enable a patient to make an informed decision. Based on interviews with genetic health care professionals, patients' reactions to receiving a genetic report that includes a positive molecular diagnosis vary, from patients feeling relieved to being frustrated that a diagnosis does not lead to a (change in) treatment.[41] This strongly indicates the necessity of discussing expectations before testing and including this topic in the informed consent. We have recommended important content for an informed consent that can be used for HTS of IPD for adult patients and children represented by their parents. Performing HTS in newborns and children leads to additional ethical debates in which no specific guidelines on this issue have been formulated.[42] Parents should be well informed about the impact of the HTS on the clinical management of their child, possibilities and limitations for genetic counseling, and the possibility of unsolicited findings before initiating the test.

In conclusion, we suggest that these ISTH Scientific and Standardization Committee for Genetics in Thrombosis and Hemostasis recommendations regarding diagnostic HTS for IPD and obtaining consent from the patient or parent are taken up by national thrombosis and hemostasis societies and adjusted to account for prerequisites that differ between countries.

## CONFLICT OF INTEREST

None of the authors have a conflict of interest related to this manuscript.

## AUTHOR CONTRIBUTIONS

All authors have contributed to the writing and critical review of this manuscript. All have approved the final version.

## ORCID

*Keith Gomez* https://orcid.org/0000-0002-8934-0700
*Andreas Greinacher* https://orcid.org/0000-0001-8343-7336
*Kathleen Freson* https://orcid.org/0000-0002-4381-2442

## TWITTER

*Kathleen Freson* @KathleenFreson

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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