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Title

Mosaic abnormalities of the skin – review and guidelines from the European Reference Network for rare skin diseases (ERN-Skin)

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Keywords

Mosaicism, post-zygotic, skin, guidelines, management, investigation, targeted therapy.
Abstract

Background: Cutaneous mosaicism is an area of Dermatology in which there has been an explosion of knowledge within the current decade. This has led to fundamental changes in the understanding of the conditions in this field, and to an ongoing paradigm shift in the approach to management of mosaic skin disorders.

Objectives: To lay out the general principles of mosaicism as they are currently understood, summarise the known cutaneous mosaic abnormalities of the skin with associated phenotypic and genotypic information, review the latest trials on targeted therapies and propose guidelines for the general approach to a suspected mosaic patient.

Methods: This was a consensus review as part of the European Reference Network project (ERN-Skin).

Conclusions: This study provides clinicians with a practical approach to the patient with suspected mosaicism, redefines mosaicism for the modern genetic era, and proposes a new classification system based on genetic mechanism.

What is already known about this topic?

- Cutaneous mosaicism is a complex field of Dermatology which encompasses most birthmarks, and many rare syndromes
- Some cutaneous patterns are known to be seen in mosaicism
- Very few treatment options are available for most mosaic abnormalities of the skin
• Recent high sensitivity genetic techniques have led to an explosion of knowledge about genotype and phenotype in the literature

What does this study add?

• Expert consensus from the European Reference Network ERN-Skin project
• Review of knowledge of the confirmed mosaic abnormalities of the skin, including cutaneous phenotype, extra-cutaneous associated features and genotype
• Proposed new classification of mosaic abnormalities of the skin by genetic mechanism
• Practical tips on correct sample collection and genetic investigation
• Review of trials of targeted therapies
• Guidelines for a practical clinical approach with suspected mosaicism

Introduction

The field of cutaneous mosaicism effectively began with the systematic phenotypic observations of Blaschko in 1901\(^1\), and the subsequent proposal that the observed patterns were due to the genetic mechanism of mosaicism by Jackson in 1976\(^2\). Fundamental concepts of cutaneous mosaicism were then elaborated by Happle, in a series of key publications since the late 1970s\(^3-5\). In particular, the concept of lethal mutations surviving by mosaicism\(^3\) has become axiomatic, and provides an explanation for why many mosaic disorders recognised in Dermatology appear to be sporadic. Over the same period of time, cohorts of patients with certain mosaic abnormalities of the skin have been studied, and
disease-specific classifications for the cutaneous findings have been proposed. These have allowed some conclusions to be drawn about clinical management, by associating cutaneous features with outcome measures, and with extra-cutaneous features. In general, however, there is a lack of robust disease-specific guidelines for cutaneous mosaic disorders, compounded by the publishing bias towards more severe cases that frequently dogs the literature on rare diseases.

Molecular proof of mosaicism has been much slower to emerge, due to the technical limitations of detecting low level mutations. Two relatively early discoveries, the causes of McCune-Albright syndrome\(^6\) and mosaic epidermolytic hyperkeratosis\(^7\), came about by astute observation of the phenotypic similarity to germline conditions, and subsequent candidate gene sequencing. Otherwise, molecular causes remained elusive until the present decade, when the advent of more sensitive DNA sequencing methods and a better understanding of mosaicism have allowed more directed candidate gene sequencing, and unbiased genome-wide screening.

The European Reference Network (https://ec.europa.eu/health/ern_en) is a European Union initiative to optimise management of patients with rare diseases. As part of the ERN-Skin project mosaic disorders has been highlighted as an area where guidelines for patient management are scarce, and new publications on genetic aetiology are appearing at a remarkable rate, making it difficult for practitioners to keep up to date. This document therefore serves as a review and consensus guideline for the general approach to the suspected mosaic patient, as is currently understood by an expert panel. In addition, we
took the opportunity to reappraise the definition of mosaicism for the modern genetic era, and propose a new classification system.

Definition of mosaic abnormalities of the skin, and of mosaic disorders

Mosaicism has traditionally been defined as the coexistence of at least two genotypes in an individual derived from a single zygote, and this was considered to be an abnormal state. It has, however, become eminently clear that we are all mosaic by this definition, due to a strikingly-high but normal post-zygotic mutation rate in utero\(^8\), and variable somatic mutation throughout life\(^9\). This definition therefore no longer delineates an abnormality. In addition, there is general consensus that small, single birthmarks are so common as to be part of the normal range rather than a disease phenotype. Therefore, we propose to define a mosaic abnormality of the skin as the coexistence of cells with at least two genotypes, by the time of birth, in an individual derived from a single zygote, and which leads to a disease phenotype\(^10\). A mosaic disorder can on the other hand be defined as the coexistence of cells with at least two genotypes, by the time of birth, in an individual derived from a single zygote, where the post-zygotic mutation has led to the whole disease phenotype. In other words, it does not include the superimposed mosaic manifestations of autosomal dominant diseases, or revertant mosaicism (see below).

Factors governing the phenotype of mosaic disorders

With genotypic diagnosis, many clinical diagnostic labels are now being found to be part of a disease spectrum\(^11,12\). This spectrum is, in general, far greater in mosaic disorders than in germline disorders, as there are many more variables which can affect the final phenotype.
A summary of the main variables which alter the phenotype in mosaic disorders is shown in Figure 1. The first key variable is the timing of the mutation during embryogenesis. For example, it is now clear that the same mutation is responsible for single capillary malformations of the port wine stain type, as well as for Sturge-Weber syndrome\textsuperscript{13}, or for a single circular sebaceous naevus and Schimmelpenning syndrome\textsuperscript{14}. The second key variable is the embryonic destiny of the cell which is hit by that mutation, elegantly demonstrated in Nature by entirely separate clinical entities produced by an identical genetic defect. For example, a mosaic $BRADF$ p.V600E mutation can lead to linear synringocystadenoma papilliferum\textsuperscript{15}, or to an arteriovenous malformation\textsuperscript{16}, or to multiple congenital melanocytic naevi\textsuperscript{17}. The timing and embryonic destiny are of course linked to some degree, and in general earlier mutations will produce a more severe phenotype and will be more likely to be associated with non-cutaneous features. Other factors which alter phenotype include the exact mutation, with clear phenotype-genotype associations demonstrated in some conditions\textsuperscript{14,18,19}, the background germline genotype\textsuperscript{20}, and of course the normal function of the gene. Lastly the pattern of gene expression is important in determining which organ systems develop clinically-important disease, and whether that expression is pre- or post-natal probably determines congenital and post-natal disease behaviour. For example, in Proteus syndrome the epidermal naevus and vascular malformations are frequently present at birth but are usually stable thereafter\textsuperscript{21,22}, in contrast to bony and soft tissue overgrowth which are usually not present at birth but progress dramatically in the postnatal period\textsuperscript{23,24}. This suggests that $AKT1$ in keratinocytes, for example, may be expressed both pre- and post-natally in a similar manner, whereas expression in bone may be predominantly after birth.
Classification of mosaic abnormalities of the skin by inheritance potential

Mosaicism has frequently been classified in clinical genetics textbooks into three categories based on inheritance potential, namely somatic only, gonadal only, and both somatic and gonadal. Gonadal mosaicism is a key concept in genetic counselling to explain recurrence of autosomal dominant diseases in sibs from asymptomatic parents. Practically-speaking, however, it is only really possible to test whether a mutation has affected the gonads in an adult male patient\textsuperscript{25,26}, by sequencing sperm with high sensitivity techniques, and even then it is rarely done. Furthermore, it is only really of value if it is known that the mutation in question is not lethal, as lethal mutations affecting the gonads could be passed on to the zygote but would lead to a miscarriage. More useful therefore is to divide mosaic abnormalities of the skin as defined above (and eventually individual causative mutations) into germline lethal, or germline heritable, on the basis of the literature. This broad but useful classification is included in the summary of mosaic disorders in Table 1.

It is worth mentioning that a truly mosaic disorder cannot be passed on as a mosaic disorder – they can only be passed on by a mutation being present in a gamete, and that a single-cell haploid gamete can only be either mutated or not mutated. If mutated it will give rise to a heterozygous zygote, and if not mutated it will give rise to a normal zygote. Thus, a mosaic disorder can only be passed on as a germline heterozygous condition, if at all. Where clinically it appears that a mosaic pattern condition is seen in successive generations (for example Blaschko-linear patterning), this is usually because the condition is in fact X-linked dominant with a germline mutation, and the mosaic pattern is due to the phenomenon of X inactivation. Well-known examples of this are incontinentia pigmenti and Goltz syndrome.
Classification of mosaic abnormalities of the skin by genetic pathogenesis

The cause of mosaic abnormalities of the skin by the definition above is a genetic mutation arising *in utero*, whether or not the resultant abnormality is visible at the time of birth. The term mutation here should be considered *sensu lato*, including various chromosomal anomalies, although their pathogenicity remains to be explained. An alternative method of classifying (and understanding) mosaic skin disorders is by the type of mutation which occurs *in utero*, in combination with knowledge of the inherited (germline) genotype of the individual (Table 2).

A schematic for visualising this proposed pathogenetic classification easily is laid out in Figure 2. We have avoided a numeric classification, however these could be numbered 0-3 left to right to fit to some degree with the Happle classification of type 1 and type 2 segmental\textsuperscript{27}. Firstly, in most cases of what we currently think of as mosaic disorders the germline genotype will be “normal” (with the caveat that not only is no germline normal, but there are certainly more predisposing skin disease genes to be found), and the autosomal dominant post-zygotic mutation will lead to a mosaic disorder phenotype. This includes mutations which are either germline-lethal and therefore not passed on, and germline-heritable mutations with potential for passing on as a heterozygote. Secondly, the germline genotype can be of an autosomal dominant mutation, which leads to a recognisable syndrome or a clear phenotype that is not only restricted to the mosaic abnormality. In this case, a second mutation leading to loss of the normal allele leads to a “superimposed” more severe and mosaic phenotype. This phenomenon has been proven at molecular level for certain diseases including Hailey-Hailey\textsuperscript{5}, Darier\textsuperscript{28}, Cowden syndrome\textsuperscript{29}, and Gorlin syndrome\textsuperscript{30}. Thirdly, there are conditions in which the germline genotype is of a
single recessive mutation, which does not confer a clinical phenotype or a recognisable syndrome itself, but where a post-zygotic second recessive mutation will lead to a mosaic disorder phenotype. A recent first published example of this at genetic level is ectodermal dysplasia skin fragility syndrome\textsuperscript{31}.

Theoretically a mosaic abnormality of the skin could also be generated by epigenetic alterations (other than the aforementioned X-inactivation due to methylation) however as this does not alter DNA genotype it would not fall within our here-proposed definition of a mosaic abnormality or disorder.

Lastly to be addressed there is the phenomenon of revertant mosaicism\textsuperscript{32}. This is not by this definition a mosaic disorder, but rather a phenomenon of phenotypic rescue within a pre-existing genetic skin disease. It can, however, also be understood in the same mechanistic way (\textbf{Figure 3}). It has so far been described on the background of an autosomal dominant germline, or an autosomal recessive germline. It can also occur theoretically occur on the background of a “normal germline”, in the context of a mosaic disorder.
Clinical assessment of the patient with a suspected mosaic disorder

Is the clinical presentation suggestive of a mosaic disorder?

Table 1 summarises the cutaneous mosaic disorders where molecular mosaicism has been confirmed in at least a proportion of cases. In practice however, the clinical presentation often does not fit with any known diagnostic group, or it may be atypical. Key features in the history and examination which are highly suggestive of a mosaic disorder in an undiagnosed patient are as follows:

1) Sporadic occurrence – no family history, even of a mild phenotype;
2) Congenital or early childhood onset;
3) Mosaic patterning on the skin - see below;
4) Variability/patchiness of the overall body phenotype – some areas affected, some not, which may involve asymmetry of body parts or of growth.

Patterns of cutaneous mosaicism

Patterns of cutaneous mosaicism were originally inferred to be mosaic, before molecular confirmation was available. Blaschko’s description of linear and whorled patterning is the most familiar image of cutaneous mosaicism\(^1\), later extended to the head by Happle\(^33\), however Blaschko also described some segmental patterns at that same time. Happle expanded and classified the mosaic cutaneous patterns into between 5 and 7 types\(^34\), 6/7 of which have now been proven to be the result of at least one mosaic disorder (with the sash pattern being the only one outstanding at this time). These patterns are likely to continue to be useful for phenotyping and documentation in a clinical setting. Recent and ongoing interpretation of patterns from an embryonic staging viewpoint, however, is beginning to
group these differently\textsuperscript{35-38}, which may allow better prediction of the chance of extracutaneous anomalies. In addition, other patterns can be seen in mosaic disorders, in particular multiple small round/ovoid pigmented lesions, so these should not be discounted if the rest of the presentation is suggestive.

**Full clinical phenotyping and high resolution photography**

It is important to document the clinical phenotype as precisely as possible, as it has become clear that this is pivotal in differentiating between diagnoses, and for directing appropriate genetic testing. It is important to extend this depth of clinical phenotyping to all body systems, as the presence of other features is often unpredictable from the cutaneous phenotype. Phenotyping, at least at first visit, should therefore include a full history, and full examination. History for a child should include detailed family history, history of previous miscarriages from the parents, history of this pregnancy, weight and condition at birth, neurodevelopmental milestones and any concerns, and a general systems enquiry. Examination should include the whole skin, as very often more minor skin findings have not been noticed or not reported, as well as the neurological, respiratory, cardiovascular, and abdominal systems. As regards growth, height, weight and head circumference should be recorded, and any limb length or girth discrepancy measured.

For a few diseases, there have been classifications proposed on the basis of the cutaneous phenotype. The most recent versions of these are referenced here, which can be used for more accurate phenotyping for the following diseases: Proteus syndrome\textsuperscript{33}, congenital melanocytic naevi\textsuperscript{39,40}, \textit{PIK3CA}-related overgrowth spectrum\textsuperscript{41,42}, facial port wine stains/Sturge-Weber syndrome\textsuperscript{36,43} and phakomatosis pigmentovascularis\textsuperscript{44}.
While written descriptions are important, a full set of clinical photographs should also be taken, where possible in a professional hospital setting. These serve to document the overall patterning of the disease, and to get detailed close ups of subtle cutaneous features. Moreover, as new phenotypic features are increasingly being described, detailed photographs are invaluable in the revisiting or classification of difficult cases.

Associated abnormalities in other organ systems

A summary of the commonest associated non-cutaneous abnormalities is included in Table 1. For a few confirmed mosaic disorders where reasonably large cohorts of patients have been studied, there is robust information on the nature and prevalence of the associated non-cutaneous features. In this category, we can include Proteus syndrome, Sturge-Weber syndrome, PIK3CA-related overgrowth spectrum disorders, phakomatosis pigmentovascularis (I, II, V, cesioflammae and cesiomarmorata types) and congenital melanocytic naevus syndrome, with the references given here as key recent publications in the relevant fields. Further work within these diagnoses is still required and ongoing, particularly with sub-stratification by genotype, as not all patients have the same causal genes. In all other proven mosaic disorders, cohort studies are lacking, and reporting of associated features is therefore likely to be subject to publication bias of more severe cases. Nonetheless, these publications serve to delineate the spectrum of disease, and to some extent to identify the organs most commonly involved.
Investigations

Blood sampling for associated non-cutaneous complications

In general, in mosaic disorders there are very few blood tests which are useful. In patients with Schimmelpenning syndrome or the intimately-related condition phakomatoses pigmentokeratotica (or other unclassifiable or overlapping epidermal naevus syndromes due to KRAS or HRAS mosaicism) metabolic bone disease can be a serious feature. In these cases, blood (and urine) for calcium, phosphate, Vitamin D, and FGF23 should be checked at least once, and both monitored and treated if found to be abnormal. Individuals with extensive naevoid epidermolytic hyperkeratosis can also be lacking in Vitamin D\textsuperscript{55}, as in other types of extensive ichthyoses, and this should be optimised, particularly if they are taking retinoids. In overgrowth syndromes such as CLOVES, Klippel-Trénaunay or Proteus syndrome, as well as venous, lymphatic, arterial, or complex vascular malformations\textsuperscript{56-59}, monitoring of clotting parameters including platelets, fibrinogen and D-dimers is recommended\textsuperscript{60}, particularly before any surgical or interventional radiology procedure, particularly in adolescents or young adults, or with an acute painful presentation.

Histology

Skin histology may be useful in the diagnosis or subclassification of mosaic skin disorders. It can sometimes help in characterisation or differential diagnosis of certain epidermal naevi, for instance to look for epidermolysis (histological feature of naevoid epidermolytic hyperkeratosis), for alternating orthokeratosis and parakeratosis in inflammatory linear verrucous epidermal naevus, or to differentiate epidermal naevi from linear porokeratosis
(cornoid lamella), although these are not totally robust measures. It can be helpful in diagnosing naevus psiloliparus in encephalocraniocutaneous lipomatosis, and sometimes basaloid follicular hamartomas in Happle-Tinschaert/Curry-Jones syndrome. It can also be helpful for subclassification of complex vascular malformations, although the combination of radiology and genetic testing with histology is more powerful than any one of these alone. It is usually diagnostic in the diagnosis of childhood vascular tumours, differentiating between congenital haemangioma, tufted haemangioma, and kaposiform haemangioendothelioma. Routine histology is not usually contributory for pigmented lesions – in melanocytic naevi the diagnosis is usually easily made clinically, and in fine and whorled Blaschko-linear hypo- or hyperpigmentation the histological findings are usually non-specific.

**Radiology/Imaging**

Radiological or imaging investigations are strongly recommended in some mosaic disorders, where cohort data are available, and whenever monitoring can be shown to alter management. In Proteus syndrome, radiological monitoring of bone growth and organomegaly is part of recommended management, individuals with cranial hyperostosis may need investigation for meningioma development, and the high incidence of thrombotic complications requires a low threshold for imaging should this be suspected clinically. Routine monitoring for tumour formation are not however recommended. In the PIK3CA-related overgrowth spectrum (PROS), brain magnetic resonance imaging (MRI) is required to diagnose cortical malformation in macrocephaly-capillary malformation-polymicrogyria syndrome (MCAP), and radiological characterisation and monitoring may be required for overgrowth and vascular malformations (independent of the genetic diagnosis),
in general dictated by the clinical symptomatology and the resultant need for intervention. Routine ultrasound monitoring for Wilms tumour has been recommended by some authors in proven cases of PROS, as in Beckwith-Wiedemann syndrome, However, the total number of cases reported is very low in PROS, and there is currently no consensus amongst experts as yet regarding repeated abdominal ultrasound screening.

Magnetic resonance imaging (MRI) of the CNS is recommended in infants with multiple congenital melanocytic naevi (CMN) and in those with new neurological symptoms at any stage, as the best prognostic indicator for adverse neurological outcomes and risk of melanoma. Ophthalmological assessment and MRI/angiography are recommended for infants with facial port wine stains affecting the forehead area or those who demonstrate neurological symptoms, to look for features of Sturge-Weber syndrome. This also applies for those with a diagnosis of phakomatosis pigmentovascularis. Doppler USS and/or MRI/MRA and/or angiography are frequently essential in the diagnosis, management and monitoring of vascular malformations and congenital childhood vascular tumours.

**Genetic testing**

**Which genetic test to order – getting the sample to the right laboratory**

Genetic investigation has been radically altered by the techniques of massively parallel sequencing also known as next generation sequencing (NGS), and whole genome copy number analysis. These are well-established techniques for germline mutations, which can be looked for from a standard blood sample. However, they have only recently come into clinical practice for mosaic mutations, and require a sample of affected tissue, for which a skin biopsy is usually the easiest. These new techniques have allowed the detection of
mosaic mutations with much higher sensitivity, which is the first crucial factor in obtaining a genetic diagnosis. Results are expressed in percentage of mutant alleles (less than the 50% expected for heterozygous mutations), which merely reflects the proportion of affected cells in the tissue sample studied, not the extent of mosaicism in a patient’s whole body. Current methods allow detection of mutant alleles as low as 1%, however traditionally all mosaic mutations have required validation by a second independent method before they can be confirmed diagnostically. This standard however is beginning to change, as NGS is so far superior to most other second methods. A summary of which type of genetic test to request for which type of mosaic abnormality of the skin is given in Table 2. Clinical utility of genetic testing in mosaic disorders remains to be carefully assessed, but it already has many implications. For a start, genetic diagnosis is usually beneficial for patients and families in coping with the disease. It is also increasingly important for genetic counselling, confirming whether the occurrence is sporadic, whether the risk of recurrence in siblings is low, and identifying whether there is a risk of transmission to the next generation in heterozygous form. Also, it may provide a rationale to consider innovative drugs specifically targeted at the molecular anomaly, which should ideally be evaluated in the context of a clinical trial.

If chromosomal level (as opposed to single gene) mosaicism is suspected, either a karyotype or fluorescent in situ hybridisation (FISH) may be required, which requires cultured cells from a fresh biopsy. This has historically been fibroblasts by default, however in certain specialist laboratories, culture of keratinocytes or melanocytes may be available. More recently, direct DNA extraction and comparative genomic hybridization (CGH) or SNP arrays have often been used for chromosomal mosaicism instead, however the data can be difficult to interpret. Very recently mosaic chromosomal mosaicism has been demonstrated
robustly from NGS data (personal communication, Vabres P.), and it is highly likely that this will be the method of choice from now on where available.

**Sampling and testing the right tissue**

The second crucial factor is to sample the right tissue, accessing the cells which actually carry the mutation. For example, culture and sequencing of fibroblasts from an area of affected skin will not reveal a mutation if the mutation was never in the fibroblasts but confined to the keratinocytes. In general, therefore, if it is not known with certainty which cell type is affected, a skin biopsy from affected skin should be taken in its entirety, and DNA extracted directly from the tissue. Only if it is already well-documented which cell type carries the mutation, such as melanocytes in the café-au-lait macules of mosaic NF1, or the same in McCune-Albright syndrome, should culture of a cell type be attempted before DNA extraction (specialist laboratories only). A 4mm punch biopsy is adequate to generate enough DNA for whole exome sequencing. The third crucial factor is that any skin biopsy for genetic testing must not be fixed in formalin. This renders genetic testing extremely difficult, or impossible, depending on the test. If DNA is to be extracted directly from the whole biopsy, the fresh biopsy should be taken immediately to the genetics laboratory on saline-soaked gauze, or put into a small vial of solution which protects nucleic acids from degradation, or snap frozen in liquid nitrogen (with appropriate training).

DNA can be extracted if necessary from formalin-fixed paraffin-embedded (FFPE) tissue, however the fixation process is known to fragment the DNA and to lead to sequencing artefacts. If, however, all that is required is sequencing for a known point mutation (for
example the typical NRAS mutation in congenital melanocytic naevi), or for use on a targeted sequencing panel designed for FFPE, these tests can be done from archival FFPE tissue if necessary to avoid a further biopsy$^{16,49,68}$. Whole exome sequencing for mosaic mutations in general is not recommended from FFPE DNA, although it is becoming more reliable.

Blood sampling for DNA extraction from leukocytes is recommended if taking a skin biopsy for genetic testing, as this can be used as control DNA in conditions where the mutation is not detectable in the blood, and it can be tested for the mosaic mutation once it is identified in the skin. Blood sampling procedures should be as locally prescribed, however if in doubt, in general DNA can be extracted from any bottle used for a full blood count, containing EDTA, and will be stable in the fridge for several days if necessary.

**Management**

**Multi-disciplinary team**

Our recommendation is that patients with rare mosaic abnormalities of the skin should ultimately be seen in a specialist centre with access to a multi-disciplinary team. Initial presentation is often to a Dermatologist or Paediatric Dermatologist, and if not, Dermatological advice should be sought for accurate clinical diagnosis. Once detailed assessments and investigations have been carried out, follow up in local services may be appropriate, depending on the individual case. Re-assessment in the specialist centre, however, should be considered at regular intervals, as this field is changing rapidly, and new management options may come to light. Ideally the patient should be registered either
locally or internationally in a rare diseases registry for the same reason, allowing contact with the patient to be re-established if, for example, relevant clinical trials of new therapies are begun.

**Malignancy risk in mosaic abnormalities of the skin**

Overall the risk of malignancy in mosaic abnormalities of the skin is low. Management guidelines for malignancy exist for a few conditions.

For sebaceous naevi it is now well-documented that, in contrast with benign tumours (such as syringocystadenoma papilliferum) that frequently arise, malignant tumours are rare, and arise principally in adulthood\(^\text{69-71}\). Routine resection of sebaceous naevi for prevention of malignancy is therefore not advocated. For other HRAS and KRAS mosaics, many of these are individual cases, and not all fit into a clear diagnostic category. They do, however, appear to carry a malignancy risk, but this is likely to be low at least in childhood.

For congenital melanocytic naevi it is well-documented that the absolute risk of melanoma in childhood is low\(^\text{50,72,73}\), but that there is an approximately 10% risk in children who have complex congenital neurological abnormalities on screening MRI after birth\(^\text{50}\). This is one of the key reasons for doing a screening MRI and this specific group should be monitored more closely, whilst all other groups can be reassured that the risk is approximately 1-2%.

Melanoma can arise in the CNS or in the skin.

For PTEN hamartoma syndrome, which can present with mosaic manifestations, new guidelines were published recently\(^\text{74}\), and pertain to the diagnosis and management of the high risk of tumours in PTEN conditions\(^\text{75}\). In general, for mosaic manifestations of germline conditions known to carry a malignancy risk in the skin, such as dominant dystrophic epidermolysis bullosa, or porokeratotic eccrine and ostial duct naevus, it could be assumed
there is a similar risk of malignancy in the affected skin of a mosaic individual, although this is not proven.

**Psychological support services and patient support groups**

Individuals affected by rare mosaic abnormalities of the skin, and their families, frequently require a substantial amount of psychological support, due to the psychosocial impact of both visible difference, and of medical complications including malignancy risk. This is often supported to some degree by the expert physicians involved, simply by delivering accurate information on diagnosis and prognosis, however the value of formal psychological support cannot be underestimated and should be offered in the multidisciplinary team setting where possible. This can be appropriate both soon after birth for parents of an affected child, and for the child at a later date, often useful at the transition into teenage years. Patient support groups (PSGs) form a vital part of the psychological and practical support network for patients and families, and access to an up to date list of relevant support groups in Europe is available here\textsuperscript{76}. In addition, PSGs often produce high quality online and in print written information on the condition in question, which can be accessed via their websites\textsuperscript{76}.

**Genetic counselling**

Sporadic mosaic disorders are caused by pathogenic mutations originating in the embryo, not transmitted by parental gametes. Hence in general the risk of recurrence in siblings is extremely low. It is possible that some families are predisposed to either postzygotic mutations, or to the development of a mosaic phenotype after such a mutation, as
suggested by a confirmed increased family history of birthmarks in some conditions, however the risk in these families for sibling recurrence would still be very low.

Mosaic forms of Mendelian disorders are however being recognised increasingly, and it is always worth checking the literature for descriptions of potential transmission to offspring, and in particular for the exact mutation. Mosaic neurofibromatosis type 1 (NF1) is the best studied, passed on as heterozygous full-blown NF1, but another well-known occurrence is of epidermolytic epidermal naevi being passed on as generalised heterozygous epidermolytic ichthyosis due to mutations in KRT1 or KRT10. More recent descriptions are mosaic dominant dystrophic epidermolysis bullosa (EB) due to a mutation in COL7A1 which was passed on as EB, and some which from their genotype could be predicted to be passed on in the germline. These include porokeratotic eccrine and ostial dermal duct naevus due to a mosaic GJB2 mutation which could be passed on as KID syndrome, keratinocytic epidermal naevus due to FGFR3 mutation which could be passed on as thanatophoric dwarfism, and keratinocytic epidermal naevus due to HRAS mutation which could rarely be passed on as Costello syndrome.

Genetic counselling for autosomal dominant disorders with a superimposed mosaic phenotype is the same as for any type of Mendelian autosomal dominant disorder. Counselling for autosomal recessive mosaic disorders would be that offspring could inherit a heterozygous carrier status, but would be highly unlikely to have the second somatic hit in required to produce a phenotype.
Genetic counselling is therefore relatively complex, and is not recommended to be attempted by Dermatologists alone, unless this is the agreed mechanism in certain countries. In general, patients and families should be referred to Clinical Genetics services for counselling by trained counsellors, provided they have an up-to-date knowledge of mosaicism, and in particular the inheritance potential of specific mutations.

**Targeted therapies for mosaic skin disorders**

With the discovery of the genetic basis of many of these conditions, the potential for targeted therapies has arrived (Figure 4). The attraction of such therapies lies in the ability to personalise these, not just to the diagnosis, but to the genetic variant responsible for the disorder in that particular individual. Indeed, both the phenotypic diagnosis and the genotype are highly likely to be important in directing therapy in the future, as has become increasingly the case in cancer therapeutics. Currently, targeted therapies for mosaic disorders are being used in one of two ways, either as part of clinical trials, or on a named-patient compassionate-use basis. Clinical trial participation is optimal, however depending on numbers of patients and the urgency of the clinical situation, this may not always be possible.

The main area of treatment of mosaic cutaneous disorders with targeted therapy so far has been in the area of vascular malformations, with the mTOR inhibitor Rapamycin. Publications thus far, however, have been largely without genotypic information. The first clinical approach was with high doses of Rapamycin (mean serum trough levels 10-15ng/ml), over a year in a large cohort of 57 patients with different types of vascular anomaly where
over 80% of patients demonstrated partial or response or stabilisation after six months. This study reported a relatively high level of changes in blood indices (27%), however there were no deaths related to the drug, and only two patients stopped the treatment due to adverse effects. A prospective non-controlled open label phase II trial of low dose Rapamycin in PIK3CA-mutation positive patients with overgrowth has shown a slight decrease in tissue volume after 6 months, but a substantial proportion of patients experienced adverse events. A recent compassionate usage study with a more targeted inhibitor, which inhibits p110α activity directly (the protein encoded by PIK3CA) rather than blocking the downstream effects, has also been promising, although assessment of efficacy and safety will require additional well-designed clinical trials.

AKT inhibitors have been considered as possible therapy for Proteus syndrome. Cellular studies confirmed that patient cells treated with an AKT inhibitor reduced the upregulation of the AKT-PI3K-mTOR pathway. Clinical trials and compassionate usage trials of the same inhibitor ARQ092 (Miransertib) are currently underway.

MEK inhibition has been used on a compassionate basis for patients with congenital melanocytic naevas syndrome with primary CNS melanoma. In the first case the drug was only begun two days before death, and the trial would not therefore be considered valid. Use of Trametinib in four patients in a subsequent study was associated with rapid and objective symptomatic improvement, which appeared to prolong symptom-free survival at least, however it was not sufficient to halt the usual progression to a fatal outcome. Trametinib has also been trialled in one case of FGFR1-mosaic encephalocraniocutaneous...
syndrome which presented with an astrocytoma, with no further growth at six months into treatment.\textsuperscript{91}

**Conclusions**

This review uses the phenotypic observational knowledge and hypotheses developed over the last century, combined with the molecular genetic knowledge from the last decade, to take an overview of mosaic abnormalities of the skin, and to review advances in therapy. We propose a systematic pathogenetic classification, which not only clarifies what has been a complex subject in the literature, but has clinical relevance for the method of investigation and for counselling of patients and their families. On this basis, guidelines are proposed for the general management of the suspected mosaic patient (Figure 5), which serve as a starting point for diagnosis and investigation, with published guidelines on individual conditions referenced for further reading.
Tables

Table 1

Summary of established mosaic disorders affecting the skin where at least one causative mosaic genotype has been confirmed at molecular level. For an explanation of the classification by inheritance potential and by molecular mechanism see the text and table 2.

<table>
<thead>
<tr>
<th>Clinical diagnosis</th>
<th>Cutaneous features</th>
<th>Commonest associated non-cutaneous features</th>
<th>Tumour risk</th>
<th>Causal genes (or chromosomal abnormality)</th>
<th>Classification by inheritance potential</th>
<th>Classification by molecular mechanism (based on current knowledge of the causative genes listed here)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arteriovenous malformations</td>
<td>Arteriovenous malformations</td>
<td>Involvement of any other organ</td>
<td>Not described</td>
<td>MAP2K1&lt;sup&gt;92&lt;/sup&gt;; KRA&lt;sup&gt;34&lt;/sup&gt;, BRAF&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Germline lethal for KRA and BRAF, not known but likely for MAP2K1</td>
<td>Post-zygotic dominant mutation in utero Germline lethal</td>
</tr>
<tr>
<td>Becker’s naevus and Becker’s naevus syndrome</td>
<td>Becker’s naevus</td>
<td>Pectoralis muscle and breast absence or underdevelopment</td>
<td>Not reported</td>
<td>ACTB&lt;sup&gt;93&lt;/sup&gt;</td>
<td>Germline lethal as far as is known</td>
<td>Post-zygotic dominant mutation in utero Germline lethal</td>
</tr>
<tr>
<td>Syndrome</td>
<td>Feature</td>
<td>Prognosis</td>
<td>Genetic Disorder</td>
<td>Inheritance Pattern</td>
<td></td>
<td></td>
</tr>
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<td>--------------------------</td>
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</tr>
<tr>
<td>Blue rubber bleb syndrome</td>
<td>Multiple venous malformations, Internal venous malformations, typically gut</td>
<td>Not reported</td>
<td>TEK</td>
<td>Post-zygotic dominant mutation in utero</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Likely germline lethal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital haemangioma</td>
<td>Congenital non-involuting or rapidly involuting haemangiomas (NICH and RICH respectively)</td>
<td>Not reported</td>
<td>GNA11, GNAQ</td>
<td>Post-zygotic dominant mutation in utero</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Germline lethal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLAPO syndrome</td>
<td>Capillary malformation, lymphatic malformation</td>
<td>Overgrowth</td>
<td>PIK3CA</td>
<td>Post-zygotic dominant mutation in utero</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td>Germline lethal</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Germline inheritance potential depends on exact mutation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLOVE(S) syndrome</td>
<td>Keratinocytic epidermal naevus, vascular malformations, lipomas</td>
<td>Overgrowth</td>
<td>PIK3CA</td>
<td>Post-zygotic dominant mutation in utero</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Germline lethal</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Germline inheritance potential depends on exact mutation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Condition</td>
<td>Clinical Features</td>
<td>Mutation</td>
<td>Inheritance</td>
<td>Notes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>----------------------------------------------------------------------------------</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Happle-Tinschert or Curry-Jones syndrome – NB</td>
<td>NB these two syndromes are likely the same entity, separately described in different specialties.</td>
<td></td>
<td></td>
<td>Post-zygotic dominant mutation in utero</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Segmental basaloid follicular hamartomas, linear hypopigmentation, Polysyndactyly, cerebral malformations, craniosynostosis, iris colobomas, microphthalmia, intestinal malrotation, dental anomalies, nail dysplasia</td>
<td>SMOH[98]</td>
<td></td>
<td>Germline inheritance potential depends on exact mutation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cutaneous hamartomas, gastrointestinal myofibromas, medulloblastoma (single case), trichoblastoma (single case)[98]</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Encephalocraniocutaneous lipomatosis/oculoectodermal (Toriello) syndrome.</td>
<td>Naevus psiloliparus Ocular abnormalities, neurodevelopmental delay, seizures, CNS lipomas</td>
<td></td>
<td>Not known</td>
<td>Post-zygotic dominant mutation in utero</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low-grade gliomas[99], dysembryoplastic neuroepithelial tumor (single case)[100], Wilms tumour (single case)[101]</td>
<td>KRAS[102]; FGFR1[103]</td>
<td>Not known, likely germline lethal</td>
<td>Likely germline lethal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extensive or atypical dermal melanocytosis</td>
<td>Extensive or atypical dermal melanocytosis Scleral melanocytosis, glaucoma Melanoma, eye or skin[104-107]</td>
<td>GNAQ[12]</td>
<td>Germline lethal</td>
<td>Post-zygotic dominant mutation in utero</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fine and whorled Blaschko-linear hyperpigmentation (or linear and whorled naevoid hypermelanosis)</td>
<td>Fine and whorled Blaschko-linear hyperpigmentation Wide phenotypic spectrum dependent on cause.</td>
<td></td>
<td></td>
<td>Germline lethal</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not reported but is a theoretical possibility given the wide range of possible causes.</td>
<td>KITLG[108]; multiple chromosomal mosaicism described</td>
<td>Potentially Mendelian – for KITLG . Chromosomal abnormalities could theoretically be passed on</td>
<td>Post-zygotic dominant mutation in utero Germline inheritance potential depends on</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Condition</td>
<td>Description</td>
<td>Phenotypic Spectrum</td>
<td>Genetic Cause</td>
<td>Post-Zygotic Dominant Mutation</td>
<td>Germline Inheritance Potential Depends on Exact Mutation</td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
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<td></td>
</tr>
<tr>
<td>Fine and whorled Blaschko-linear hypopigmentation (previously within hypomelanosis of Ito)</td>
<td>Fine and whorled Blaschko-linear hypopigmentation</td>
<td>Wide phenotypic spectrum dependent on cause. For MTOR cases – hemimegalencephaly.</td>
<td>Rare, but various described(^{109-111}) (none so far with MTOR. Again is likely to depend on individual genetic cause)</td>
<td>MTOR(^{114}), multiple chromosomal mosaicism described</td>
<td>Potentially Mendelian – for MTOR (Smith-Kingsmore syndrome). Chromosomal abnormalities could theoretically be passed on</td>
<td></td>
</tr>
</tbody>
</table>

| Kaposiform haemangioendothelioma                                           | Kaposiform haemangioendothelioma                                              | Kasabach-Merritt phenomenon | Not reported although locally aggressive | GNA14\(^{114}\) Not known | Not known |

| Keratinocytic FGFR3 epidermal naevus syndrome                              | Blaschko-linear keratinocytic epidermal naevus                              | Craniofacial dysmorphism, neurological abnormalities | Not reported | FGFR3\(^{114}\) Potentially Mendelian – theoretically could be passed on as thanatophoric dwarfism dependent on mutation | Post-zygotic dominant mutation in utero |

<p>| Keratinocytic KRAS epidermal naevus syndrome                               | Blaschko-linear keratinocytic epidermal naevus                              | Polycystic renal disease | Rhabdomyosarcoma | KRAS(^{115}) Germline lethal | Post-zygotic dominant mutation in utero |</p>
<table>
<thead>
<tr>
<th>Condition</th>
<th>Lesion Description</th>
<th>Associated Features</th>
<th>Gene(s)</th>
<th>Disease Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linear naevus comedonicus</td>
<td>Linear naevus comedonicus, acne</td>
<td>Not reported</td>
<td>Not reported</td>
<td>FGFR2&lt;sup&gt;116&lt;/sup&gt; Potentially Mendelian, dependent on mutation could be passed on as Apert’s syndrome</td>
</tr>
<tr>
<td>Linear syringocystadenoma papilliferum</td>
<td>Linear syringocystadenoma papilliferum</td>
<td>Ocular abnormalities</td>
<td>Astrocytoma in single case&lt;sup&gt;117&lt;/sup&gt;</td>
<td>BRAF&lt;sup&gt;115&lt;/sup&gt; Germline lethal</td>
</tr>
<tr>
<td>Lymphatic malformations /generalised lymphatic anomaly</td>
<td>Lymphatic malformations /generalised lymphatic anomaly</td>
<td>Involvement of any other organ</td>
<td>Not reported</td>
<td>PIK3CA&lt;sup&gt;118&lt;/sup&gt;; NRAS&lt;sup&gt;119&lt;/sup&gt; Potentially Mendelian dependent on mutation NRAS – germline lethal as far as is known</td>
</tr>
<tr>
<td>Macrocephaly-capillary malformation syndrome</td>
<td>Reticulate capillary malformation</td>
<td>Macrocephaly, neurological abnormalities, overgrowth</td>
<td>Wilms tumour</td>
<td>PIK3CA&lt;sup&gt;68&lt;/sup&gt; Potentially Mendelian dependent on the mutation</td>
</tr>
</tbody>
</table>

Germline lethal

Post-zygotic dominant mutation in utero

Germline inheritance potential depends on exact mutation
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Clinical Features</th>
<th>Pathogenicity Description</th>
<th>Genes</th>
<th>Inheritance Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>McCune-Albright syndrome</td>
<td>Segmental or broad Blaschko-linear café-au-lait macular hyperpigmentation, pigmentation of oral mucosa</td>
<td>Polyostotic fibrous dysplasia, autonomous endocrine overactivity</td>
<td>Overall incidence of all types &lt;1%&lt;sup&gt;120&lt;/sup&gt;</td>
<td>GNAS&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mosaic dominant dystrophic epidermolysis bullosa</td>
<td>Linear blistering</td>
<td>Not reported</td>
<td>Not reported</td>
<td>COL7A1&lt;sup&gt;81&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mosaic Legius syndrome</td>
<td>Café-au-lait macules, freckling. Likely could be localised or generalised.</td>
<td>Not reported</td>
<td>Not reported</td>
<td>SPRED1&lt;sup&gt;122&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mosaic neurofibromatosis type 1 (NF1) (localised or generalised)</td>
<td>Either localised/segmental café-au-lait macules, freckling, or cutaneous neurofibromas, or generalised low levels of same features</td>
<td>Neurodevelopmental abnormalities, epilepsy, bony abnormalities</td>
<td>Neurofibromas common, Hodgkin’s lymphoma (single case), ganglioneuroblastoma (single case)&lt;sup&gt;122&lt;/sup&gt;</td>
<td>NF1&lt;sup&gt;27,123&lt;/sup&gt;</td>
</tr>
<tr>
<td>Multiple congenital</td>
<td>Congenital melanocytic</td>
<td>Neurological</td>
<td>Melanoma, CNS or</td>
<td>NRAS&lt;sup&gt;24&lt;/sup&gt;;</td>
</tr>
</tbody>
</table>

Germline inheritance potential depends on exact mutation

Post-zygotic dominant mutation in utero

Germline lethal

Germline heritable

Germline heritable

Germline heritable

Germline heritable

Germline heritable

Germline heritable

Germline heritable

Germline heritable

Germline heritable

Germline heritable

Germline heritable

Germline heritable

Germline heritable
<table>
<thead>
<tr>
<th>Condition</th>
<th>Phenotype</th>
<th>Overview</th>
<th>Mutation</th>
<th>Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>melanocytic naevi (CMN) or CMN syndrome</td>
<td>naevi</td>
<td>abnormalities, characteristic facial features, subtle endocrinological disturbances, skin, incidence varies with phenotype 1-12%, rarely rhabdomyosarcoma</td>
<td>BRAF(^{17})</td>
<td>dominant mutation in utero</td>
</tr>
<tr>
<td>Naevoid epidermolytic hyperkeratosis</td>
<td>Keratinocytic epidermal naevus</td>
<td>Not reported, Not reported</td>
<td>KRT10; KRT1(^{125})</td>
<td>Post-zygotic dominant mutation in utero</td>
</tr>
<tr>
<td>Naevus comedonicus</td>
<td>Naevus comedonicus</td>
<td>Not reported, Not reported</td>
<td>NEK9(^{126})</td>
<td>Post-zygotic dominant mutation in utero</td>
</tr>
<tr>
<td>Papillomatous pedunculated sebaceous naevus</td>
<td>Papillomatous pedunculated sebaceous naevus</td>
<td>Not reported, Not reported</td>
<td>FGFR2(^{127})</td>
<td>Post-zygotic dominant mutation in utero</td>
</tr>
<tr>
<td>Parkes-Weber syndrome</td>
<td>Arteriovenous</td>
<td>Central nervous</td>
<td>RASA1(^{128})</td>
<td>Post-zygotic dominant mutation in utero</td>
</tr>
</tbody>
</table>

\(^{17}\) BRAF mutation is associated with a higher risk of developing rhabdomyosarcoma.

\(^{125}\) KRT10 and KRT1 mutations are associated with epidermolytic ichthyosis.

\(^{126}\) NEK9 mutation is associated with a post-zygotic dominant mutation in utero.

\(^{127}\) FGFR2 mutation is associated with a post-zygotic dominant mutation in utero.

\(^{128}\) RASA1 mutation is associated with a Mendelian genetic inheritance.
<table>
<thead>
<tr>
<th>Phakomatosis pigmentokeratotica</th>
<th>Naevus spilus, keratinocytic epidermal naevus, rarely congenital melanocytic naevus, woolly hair naevus</th>
<th>Overgrowth (rare), congenital skeletal abnormalities, Vitamin D resistant hypophosphataemia</th>
<th>Rhabdomyosarcoma (^{129}), HRAS (^{129}), KRAS (^{129}), BRAF (^{131})</th>
<th>Potentially Mendelian – theoretically could be passed on as Costello syndrome, or Cardio Facial Cutaneous syndrome dependent on mutation</th>
<th>Post-zygotic dominant mutation in utero</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phakomatosis pigmentovascularis, (cesioflammea, cesiomarmorata and achromiomelanomarmorata types)</td>
<td>Capillary malformations (port wine stain/naevus flammeus, or reticulate, with or without naevus anaemicus)</td>
<td>Glaucoma, neurological vascular abnormalities, overgrowth or undergrowth</td>
<td>Melanoma, eye or skin (^{132,133})</td>
<td>GNA11, GNAQ (^{132})</td>
<td>Germline lethal</td>
</tr>
<tr>
<td>Phylloid hypermelanosis</td>
<td>Phylloid pattern hyperpigmentation</td>
<td>Craniofacial dysmorphism, neurological abnormalities, skeletal abnormalities, eye anomalies, sensorineural hearing loss, cicatricial alopecia, tooth abnormalities</td>
<td>Not reported</td>
<td>Copy number changes affecting chromosome 13q (^{134}), or 5p (^{135})</td>
<td>Chromosomal abnormalities could be passed on in the germline – lethality would depend on the exact change</td>
</tr>
<tr>
<td>Phylloid hypomelanosis</td>
<td>Phylloid pattern</td>
<td>Neurodevelopmental</td>
<td>Not reported</td>
<td>Copy number changes affecting chromosome 13q (^{134}), or 5p (^{135})</td>
<td>Chromosomal abnormalities could be passed on in the germline – lethality would depend on the exact change</td>
</tr>
</tbody>
</table>

second hit or loss of normal allele in utero
Germline heritable

Post-zygotic dominant mutation in utero
Germline inheritance potential depends on exact mutation

Phakomatosis pigmentovascularis, (cesioflammea, cesiomarmorata and achromiomelanomarmorata types)

Phylloid hypermelanosis

Phylloid hypomelanosis

Phylloid hypomelanosis
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Clinical Features</th>
<th>Genetic Basis</th>
<th>Inheritance Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porokeratotic eccrine and ostial dermal duct naevus</td>
<td>Hypopigmentation, delay, conductive hearing loss, short stature, skeletal abnormalities, asymmetric growth, craniofacial abnormalities, choroidal and retinal coloboma</td>
<td>Chromosome 13q abnormalities could be passed on in the germline – lethality would depend on the exact change</td>
<td>Dominant mutation <em>in utero</em></td>
</tr>
<tr>
<td>Proteus syndrome</td>
<td>Keratinocytic epidermal naevus, vascular malformations, lipomas, cerebriform connective tissue naevus</td>
<td>Squamous cell carcinoma</td>
<td>Post-zygotic dominant mutation <em>in utero</em></td>
</tr>
<tr>
<td>PTEN hamartoma or Cowden syndrome or SOLAMEN syndrome</td>
<td>Keratinocytic epidermal naevus, connective tissue naevi, lipomas, macrocephaly, other overgrowth, dysmorphic facies</td>
<td>Multiple benign and malignant tumours</td>
<td>Mendelian Post-zygotic second hit or loss of normal genetic material</td>
</tr>
<tr>
<td>Genetic Syndrome</td>
<td>Clinical Features</td>
<td>Genetic Changes</td>
<td>Inheritance</td>
</tr>
<tr>
<td>------------------</td>
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<td>-------------</td>
</tr>
<tr>
<td>Sebaceous naevus syndrome/Schimmelpenning syndrome</td>
<td>Linear sebaceous naevi, rarely lymphatic malformations(^1), Skeletal, neurological, ophthalmological abnormalities, Vitamin D resistant hypophosphataemia, Trichoblastoma, syringocystadenoma papilliferum; malignancy rare, basal cell carcinoma</td>
<td>HRAS, KRA(S)(^2)</td>
<td>Germline heritable</td>
</tr>
<tr>
<td>Sturge-Weber syndrome</td>
<td>Capillary malformations (port wine stain/naevus flammeus), Glaucoma, neurological vascular abnormalities, overgrowth or undergrowth</td>
<td>GNA(Q)(^3)</td>
<td>Germline lethal</td>
</tr>
<tr>
<td>Tufted angioma</td>
<td>Tufted angioma, Kasabach-Merritt phenomenon</td>
<td>GNA(A14)(^3)</td>
<td>Not known</td>
</tr>
<tr>
<td>Woolly hair naevus</td>
<td>Woolly hair naevus, epidermal naevus, agminated melanocytic naevi, Focal cortical dysplasia, cerebral cavernous malformation (single case)</td>
<td>HRAS(^4)(^5), BRAF(^1)(^3)</td>
<td>Germline lethal</td>
</tr>
</tbody>
</table>

\(^1\) References: 141
\(^2\) References: 14
\(^3\) References: 13
\(^4\) References: 131
\(^5\) References: 132
Table 2

Proposed classification of mosaic abnormalities of the skin, by genetic pathogenesis and inheritance potential, and rule-of-thumb guidelines for the type of genetic testing to order. For sample preparation see text for details.

<table>
<thead>
<tr>
<th>Classification of mosaic abnormality of the skin by inheritance potential</th>
<th>Suspected genetic mechanism of the mosaic abnormality of the skin in the affected individual</th>
<th>A classical example</th>
<th>Classified as a mosaic disorder of the skin?</th>
<th>Samples to take if genetic investigation required or desired</th>
<th>Sample preparation and testing type to request</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autosomal dominant mosaic abnormality of the skin, germline lethal</td>
<td>“Normal” germline genotype. Single heterozygous post-zygotic pathogenic mutation in utero, resulting in mosaic disorder of the skin, which would be lethal in the germline and therefore not passed on to future generations.</td>
<td>Proteus Syndrome (^{19})</td>
<td>Yes</td>
<td>Skin biopsy for diagnosis, blood sample for comparison (or in case of McCune-Albright or MCAP may pick up mutation in blood or saliva)</td>
<td>For single gene disorders – direct DNA extraction from skin biopsy and DNA sequencing by high sensitivity method (unless cell culture of correct cell type available) For chromosomal abnormalities – either direct DNA extraction from skin biopsy, with microarray or preferably next generation sequencing for copy number changes, or cell culture of appropriate cell and karyotype with mosaicism screen</td>
</tr>
<tr>
<td>Autosomal dominant mosaic abnormality of the skin, germline heritable</td>
<td>“Normal” germline genotype. Single heterozygous post-zygotic pathogenic mutation in utero, resulting in mosaic disorder of the skin, which could be tolerated in the germline and therefore with potential for transmission as a heterozygous autosomal dominant</td>
<td>Segmental mosaic neurofibromatosis type 1 (^{77})</td>
<td>Yes</td>
<td>Skin biopsy, blood sample, possibly cheek swab (can be useful in PIK3CA mutations with MCAP phenotype, and in generalised mosaic NF1)</td>
<td>For single gene disorders – direct DNA extraction from skin biopsy and blood (and cheek swab), with DNA sequencing by high sensitivity method (unless cell culture of correct cell type available) For chromosomal abnormalities – either direct DNA extraction from skin biopsy and blood, with microarray or preferably next</td>
</tr>
<tr>
<td>Autosomal dominant condition, germline heritable, with mosaic component superimposed</td>
<td>Single dominant mutation in the germline, either inherited or \emph{de novo}, which leads to a recognisable disease phenotype/syndrome in the patient independent of the mosaic skin phenotype. Post-zygotic second-hit pathogenic mutation \emph{in utero}, loss of heterozygosity, and resultant superimposed mosaic pattern, in the context of a wider phenotype of a recognised inherited syndrome.</td>
<td>Hailey-Hailey disease\textsuperscript{5}</td>
<td>No – superimposed mosaic manifestation of autosomal dominant condition</td>
<td>Blood sample for diagnosis. Skin biopsy only if wish to investigate mechanism for superimposed mosaic pattern</td>
<td>DNA extraction from blood sample, with standard DNA sequencing</td>
</tr>
<tr>
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<td></td>
</tr>
<tr>
<td>Autosomal recessive mosaic abnormality of the skin, germline carrier status heritable</td>
<td>Single recessive mutation in the germline which leads to no recognisable phenotypic manifestations \emph{per se}. Post-zygotic second-hit pathogenic mutation \emph{in utero}, resulting in mosaic disorder of the skin, and which is the only manifestation of the disease – i.e. it is not part of a recognised phenotype/syndrome. Could not be passed on.</td>
<td>Ectodermal dysplasia skin fragility syndrome\textsuperscript{31}</td>
<td>Yes</td>
<td>Skin biopsy and blood sample if wish to investigate mechanism</td>
<td>DNA extraction from blood sample, with standard DNA sequencing. Direct DNA extraction from skin biopsy, with DNA sequencing by high sensitivity method</td>
</tr>
</tbody>
</table>
Figures

Figure 1
Principal variables which contribute to the unique phenotype of a mosaic disorder of the skin in any one individual.

Figure 2
Schematic representing the molecular mechanisms which underlie mosaic abnormalities of the skin, including mosaic disorders (lethal and non-lethal in the germline) superimposed mosaic manifestations of dominant Mendelian disorders and mosaic presentations of recessive Mendelian disorders.

Figure 3
Schematic representing the molecular mechanisms which underlie revertant mosaicism, not classified as a mosaic disorder as it is a phenomenon of phenotypic rescue.

Figure 4
Schematic of the main intracellular signalling pathways involved in mosaic disorders, with potential drug targets indicated.

Figure 5
Patient pathway - practical management flow chart for the suspected mosaic patient
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