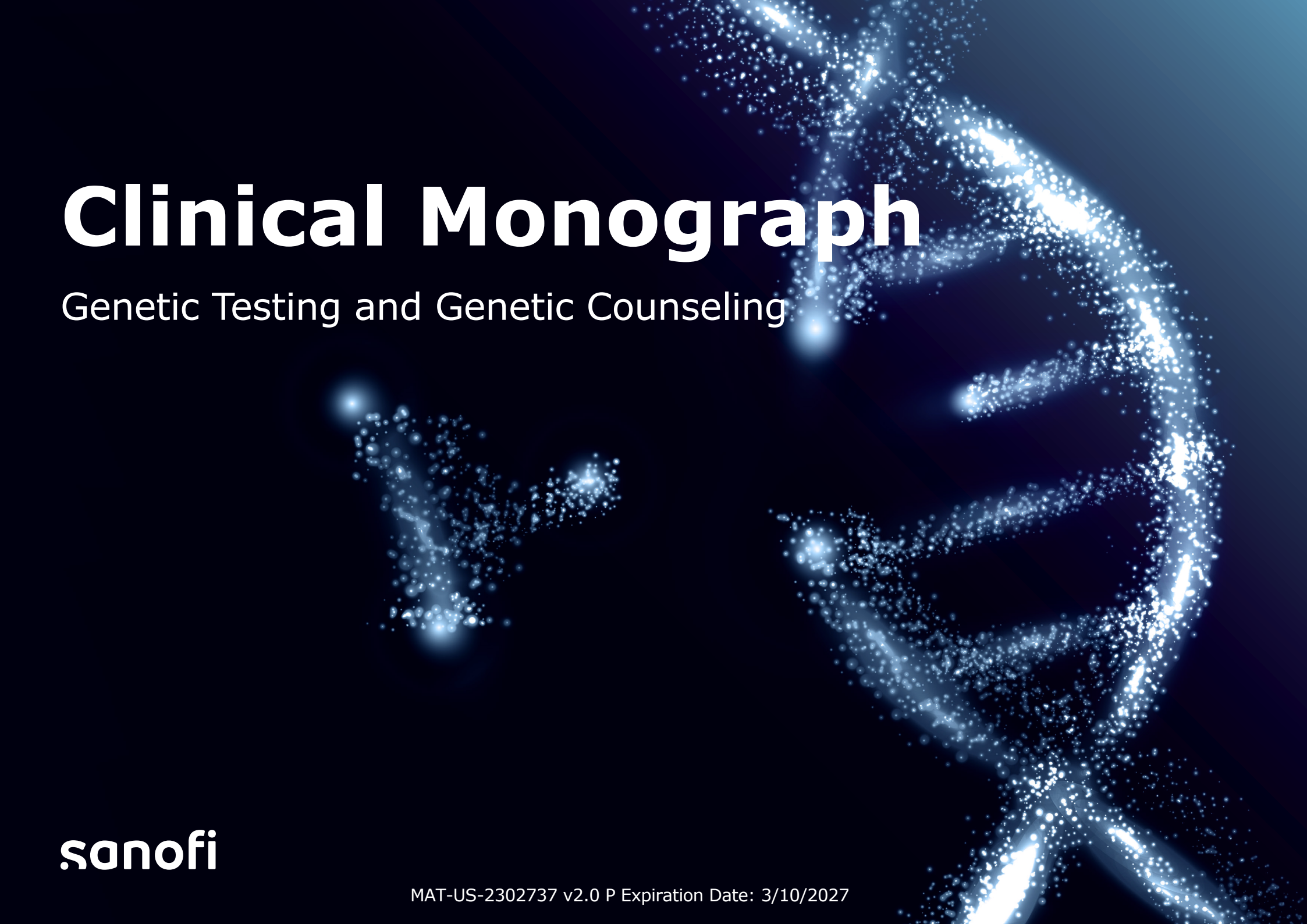
Clinical Monograph

Genetic Testing and Genetic Counseling



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The 2022 Rare Disease Advisory Council Meeting

In August 2022, the Sanofi Rare Disease Team conducted an Advisory Council Meeting to bring together experienced advanced practice providers (APPs) from various regions throughout the United States. The purpose of this meeting was to establish a network for education and communication to help advance patient care by sharing insights, resources, and best practices for genetic testing and providing genetic counseling. The feedback from this meeting provided a basis for initiatives such as monographs, newsletters, and other educational material available to APPs through the Sanofi Rare Disease Medical Team. The Rare Diseases Advisory Council also helped identify knowledge gaps, educational resource needs, and potential topics for future initiatives, as part of Sanofi's ongoing commitment to APPs in their care of patients with rare diseases. This monograph contains the views, recommendations, and real-world experience of the attendees of the APP Advisory Council and does not necessarily reflect the views of Sanofi.

Sanofi compensated participants for their participation in the meeting.

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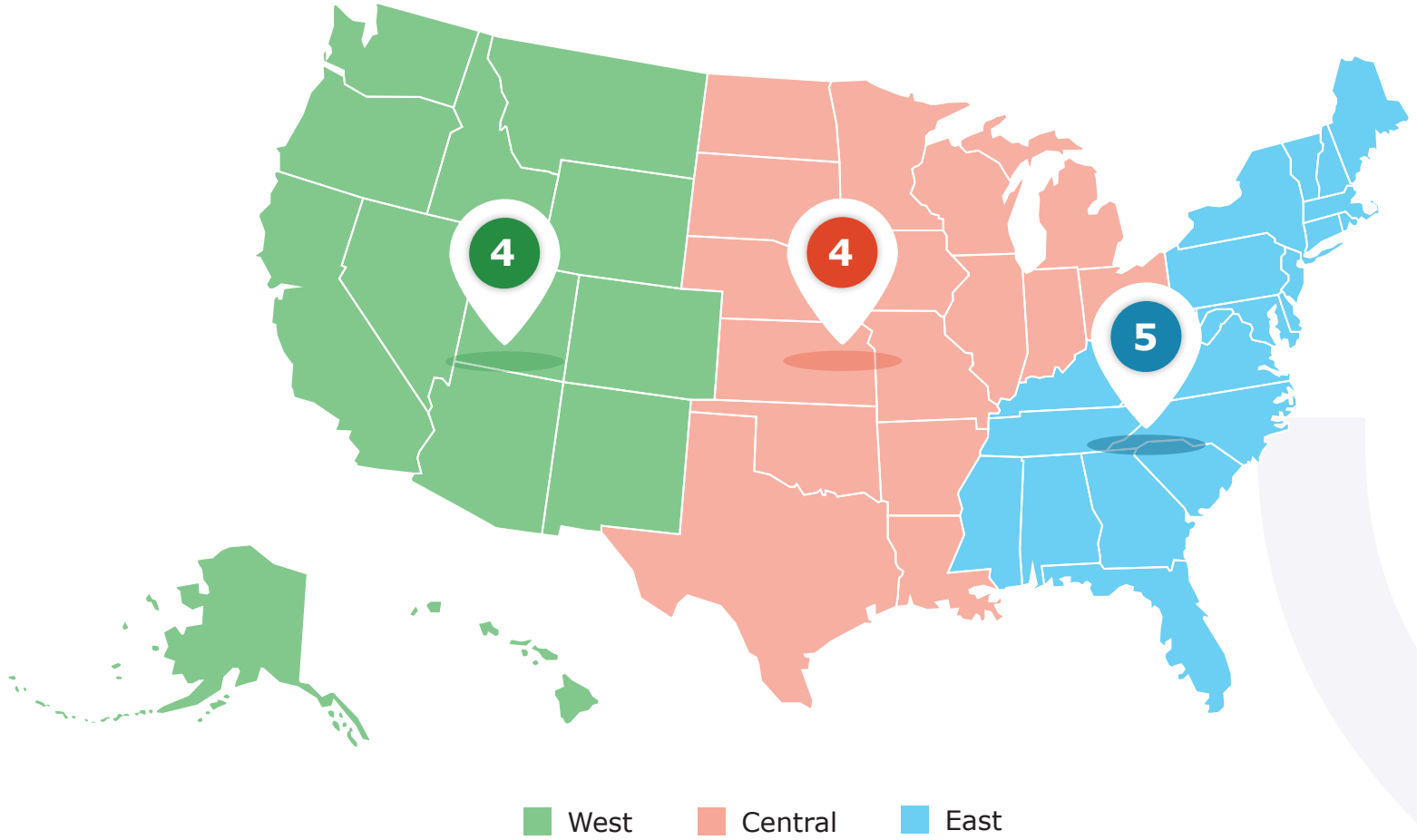

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Introduction to Genetic Testing and Counseling

Genetic testing has become increasingly relevant across the spectrum of healthcare. In recent years, genetic testing has become less expensive and less time consuming and therefore, much more accessible to clinicians and their patients. However, testing is not always a straightforward process, as some genetic diseases show a wide variety of phenotypes and/or are genetically complex in nature (**Table 1**).[1,2] This makes interpretation of genetic testing results difficult in some cases.

As genetics and genomics become more integrated into everyday healthcare, more and more healthcare providers (HCPs) are expected to have knowledge about genetic diseases and testing. Despite significant advances in relevant research and knowledge, education for HCPs has remained largely unchanged over the last several decades. A recent study showed that only about 15% of surveyed medical residents were satisfied with their training on initiating a basic genetic workup.[3] Among the Advisory Council members, most agreed that they had little to no formal training in genetics. Much of their knowledge had come from consulting journal articles, textbooks, online courses, or their colleagues in genetics.

TABLE 1: GLOSSARY OF TERMS

Allele	Alternate forms of the same gene at a particular locus with small differences in the sequence of DNA bases
Amino acid	Building block of protein; each amino acid is encoded by a set of three nucleotides within a gene
Autosomal dominant disorder	Conditions that are clinically apparent in the heterozygous state; when one allele at a particular genetic locus is a pathogenic variant
Autosomal recessive disorder	Conditions that are clinically apparent only in the homozygous or compound heterozygous state; both alleles at a particular genetic locus are pathogenic
Autosomes	The first 22 pairs of chromosomes; these are the same in males and females
Benign variant	A variant with an allele frequency above 1% that is generally assumed to be normal human variation and not causative of a Mendelian genetic condition
Chromosomes	The large structure of organized genes
Compound heterozygous	Having two different abnormal alleles at a particular locus, one on each chromosome of a pair; usually refers to individuals affected with an autosomal recessive disorder
Deletion	A sequence change where, compared with a reference sequence, one or more nucleotides are not present (deleted)
Deoxyribonucleic acid (DNA)	The molecule that encodes the genes responsible for the structure and function of an organism and allows for transmission of genetic information from one generation to the next. The information in DNA is stored as a code made up of four chemical bases (nucleotides): adenine (A), guanine (G), cytosine (C), and thymine (T)
Duplication	A sequence change where, compared with a reference sequence, a copy of one or more nucleotides are inserted into that sequence
Exon	Areas of the gene destined to be represented in messenger ribonucleic acid (mRNA) coding sequences
Frame shift	Shift in the grouping of nucleotides that changes the code for amino acids
Gene	Basic physical and functional unit of heredity
Genotype	A person's genetic constitution, collectively, or typically referring to a single locus (gene)
Hemizygous	The situation in which an individual has only one member of a chromosome pair or chromosome segment rather than the usual two; refers in particular to X-linked genes in males who under normal circumstances have only one X chromosome
Heterozygous	Having two different alleles at a particular locus, one on each chromosome of a pair
Homozygous	Having two identical alleles at a particular locus, one on each chromosome of a pair
In-frame	Mistakes in the DNA that cause the number of nucleotides to stay constant (or in multiples of 3) does not change the amino acid sequence
Insertion	A sequence change where, compared with the reference sequence, one or more nucleotides are inserted
Intron	Areas of DNA between exons; they are initially transcribed but are not present in the final protein product
Pathogenic variant	A permanent change in the nucleotide sequence that is generally assumed to be disease causing
Phenotype	Observable expression of the genotype
Reduced Penetrance	When some individuals with a disease-causing variant in a gene develop the disease while others don't
Sex chromosomes	The 23rd pair of chromosomes, females usually have two X chromosomes, males usually have one X and one Y chromosome
Substitution	A sequence change where, compared with a reference sequence, one nucleotide is replaced by one other nucleotide
Variant of uncertain (or unknown) significance (VUS)	A permanent change in the nucleotide sequence that is not currently able to be defined as either benign or disease causing
X-linked disorders	Genes responsible for these conditions are located on the X chromosome. Phenotypic manifestations may differ between males and females

Source: National Institutes of Health National Human Genome Research Institute. Talking Glossary of Genetic and Genomic Terms. Available at: https://www.genome.gov/genetics-glossary.

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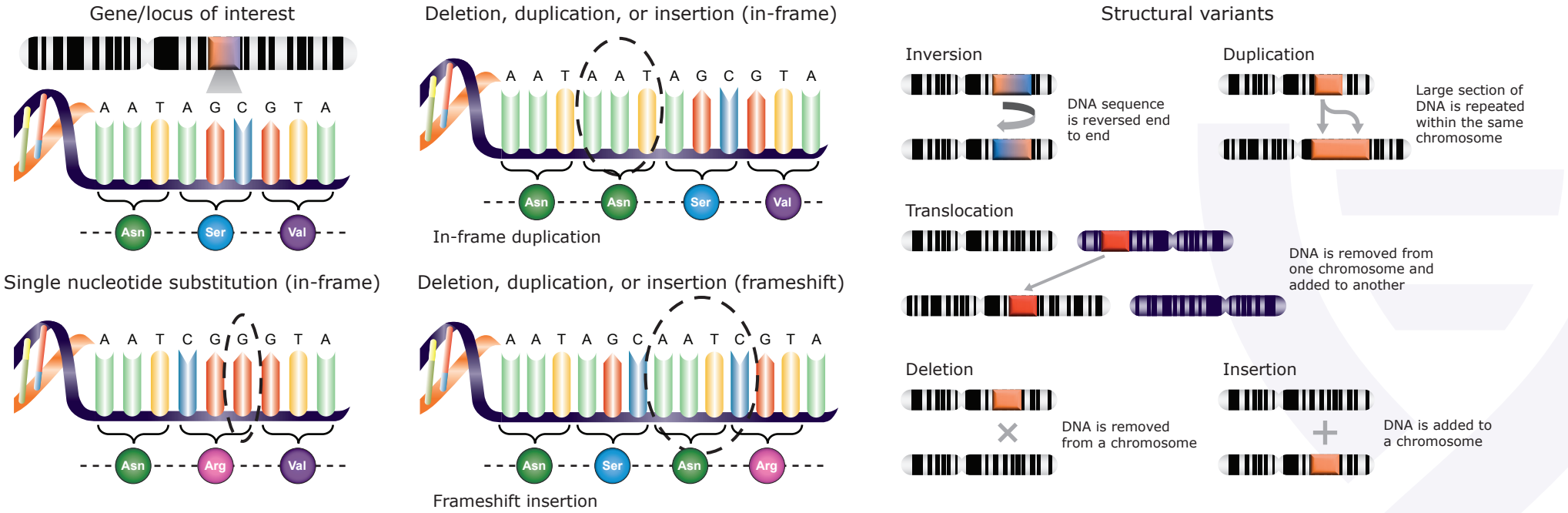
Genetic Testing – Selecting the Right Test

Within the human genome there are approximately 3 billion DNA nucleotides, 20 million of which may be altered without major health implications. Of the approximately 20 thousand genes within the human genome, nearly 4000 have been implicated in disease. A variety of alterations to the genome can occur, including single nucleotide variants (SNVs), small insertions or deletions, and structural variants (**Figure 1**). The vastness of the human genome and the variations within it can present a significant challenge in diagnostic genetics to identify which variants are disease causing.[2]

FIGURE 1: TYPES OF GENETIC SEQUENCE CHANGES[2]



Several genetic testing modalities are frequently used in a clinical setting. These include Sanger sequencing, chromosomal microarray (CMA), and next-generation methodologies including whole-genome sequencing (WGS), whole-exome sequencing (WES), and targeted, next-generation sequencing (NGS) panels (**Table 2**).[2]

Sanger sequencing has long been considered the gold standard of genetic sequencing due to its accuracy in detecting SNVs, deletions, and duplications. Sanger sequencing can be used to confirm a molecular diagnosis for single-gene disorders and findings detected using NGS (**Table 2**).[2] However, due to cost, the Sanger technique is no longer used for routine sequencing.

CMA, which includes array comparative genomic hybridization and single-nucleotide polymorphism arrays, offers genome-wide coverage and can be used to examine clinically relevant regions at the exon level (**Table 2**).[2]

NGS is a 'massively parallel' sequencing technology that can simultaneously sequence multiple DNA regions. NGS has the the ability to read nucleotides from an entire genome (WGS), from all of the coding regions within the genome (WES), or from targeted regions containing genes of interest (targeted panels). As the expense of genome sequencing has decreased steadily over the years and technology has improved, NGS has become more accessible and cost-effective for a broader population (**Table 2**).[2] Due to these advantages, NGS is the most common methodology of sequencing used currently.

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Advisors had diverse opinions on what situations may warrant ordering WES. Some clinicians noted that they only order WES as a follow-up to initial negative panel findings.

TABLE 2: INDICATIONS, ADVANTAGES, AND LIMITATIONS FOR GENETIC TESTING MODALITIES[2,4]

Test	Scope and Indication	Advantages	Limitations
Chromosomal microarray (CMA)	• Detects copy number variants resulting in large deletions and duplications • Used when a chromosomal deletion or duplication syndrome is suspected	• Genome wide	• Cannot detect SNVs and small copy number variants • Limited ability to detect balanced chromosomal rearrangements
Site-specific analysis	• Detects a single known variant, typically a private pathogenic variant that was previously found in a family member	• Fast turn-around time • Low cost • Minimal risk of VUS • No risk of incidental findings	• Does NOT examine entirety of gene in question • May potentially miss other variants within that gene
Sanger sequencing	• Detects SNVs and small deletions/ duplications within a single gene • Used when a single-gene disorder is suspected	• Highly accurate • Faster turn-around compared with NGS • Minimal risk of VUS • No risk of incidental findings	• Cannot detect larger deletions and duplications • Less time- and cost-efficient compared with NGS
Targeted NGS panel	• Detects SNVs and small deletions/ duplications in selected genes of interest • Used when there are multiple genes associated with a phenotype	• Panels can be customized to include specific genes of interest • Testing region can be customized to ensure sufficient coverage in the targeted region • Lower risk of VUS and incidental findings compared with WES or WGS	• Lower diagnostic sensitivity for heterogenous disorders compared with WES/WGS • Requires additional sequencing for any genes outside of the targeted regions with any new clinical signs or symptoms
WES/WGS	• Detects SNVs and small deletions/ duplications within all ~20,000 genes • Used when multiple nonspecific features are present or with cases of extreme heterogeneity	• Unbiased approach to sequencing • Higher diagnostic sensitivity compared with targeted panels or single gene testing • Most time– and cost-efficient modality of sequencing • Does not need additional sequencing with new clinical signs or symptoms	• High likelihood of VUS and incidental findings • Higher potential risk of breach of confidentiality with inadequate storage of results and data • Due to the large amount of genomic data surveyed, WES/WGS can miss variants that would be identified by more targeted testing

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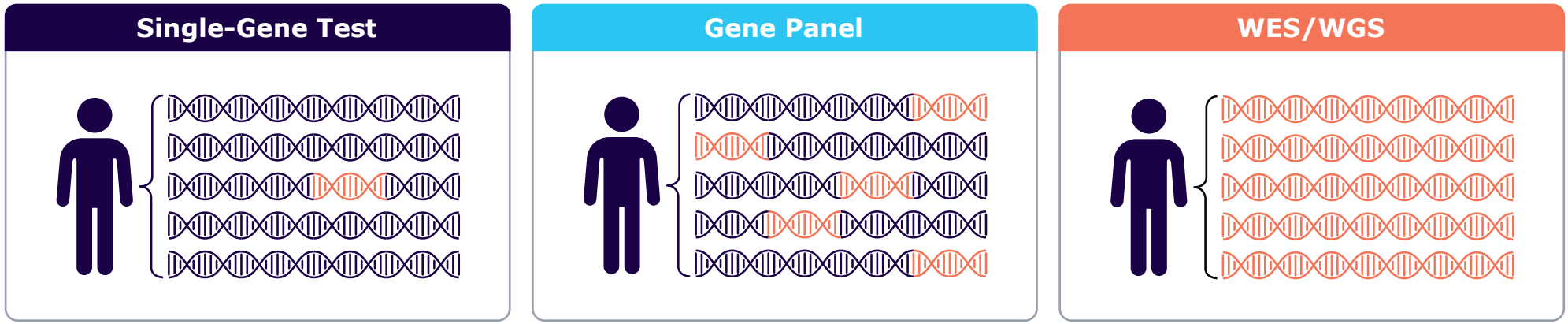

WES=whole-exome sequencing; WGS=whole-genome sequencing.

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Advisors noted that several factors can influence the type of testing that is ordered for the patient. Many advisors opt for sponsored gene panels and select specific genes that they want tested, which helps narrow down what would be a large amount of information.

Factors that may influence type of genetic testing ordered by advisors

- **Availability of in-house testing**
- **Specific patient population**
- **Insurance coverage and out-of-pocket costs**

Biochemical Testing in Genetic Disease

Biochemical testing is often used to complement genetic testing when investigating a diagnosis for genetic disease. In genetic diseases that are not attributed to a single gene, or that present with highly heterogenous phenotypes, biochemical testing may be needed to confirm the diagnosis. In lysosomal storage disorders, testing for enzyme activity can help clarify genetic results. For example, a low acid β-glucosidase (β-glucocerebrosidase) enzyme activity result is highly suggestive of a diagnosis of Gaucher disease, even if the patient does not have two pathogenic allele variants found in their genetic sequencing. Furthermore, these tests are essential for treatment monitoring, clinical management, and as follow-up to abnormal newborn screening cases. Biochemical testing often includes assays that investigate enzyme activity and levels of metabolites, such as glycosaminoglycans and glycosphingolipids.[5]

Pre-test Counseling

Genetic counseling is the process of helping people understand and adapt to the medical, psychological, and familial implications of genetic contributions to disease. This process integrates the following:

1. Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence.
2. Education about inheritance, testing, management, prevention, resources, and research.
3. Counseling to promote informed choices and adaptation to the risk or condition.

Before genetic testing takes place, HCPs should counsel the patient on the pros and cons of genetic testing, how the testing will take place, insurance coverage and out-of-pocket costs of the testing, potential implications to life insurance and disability coverage, rights regarding health insurance and employment, results disclosure, and potential results of the testing (**Table 3**). Genetic counseling on these topics is critical to ensure that patients are sufficiently educated about the implications of genetic testing. Guiding the patient through these topics before they receive genetic testing helps allows the patient to make well-informed decisions.[6]

TABLE 3: PRE-TEST COUNSELING AND INFORMED CONSENT TOPICS AND IMPORTANCE[2,7-11]

Topic	Importance
Pros and cons of genetic testing 	• Patient awareness of health-related impacts such as healthy behaviors, avoiding risk factors, and avoiding unnecessary medical treatment • Understanding the impact that results could have on themselves and family members/offspring • Understanding non-health-related impacts, including psychosocial and societal
Type of testing and information gained from testing 	• Patient understanding the difference between prognostic, diagnostic, and carrier screening tests • Patient understanding the type of testing they are receiving (eg, single-gene test, gene panel, WES/WGS) and how it relates to the disease in question • Patient understanding of what information they may not receive (eg, genes of uncertain clinical utility on WES/WGS, limited evidence regarding penetrance) • Patient awareness of what a positive, negative, or uncertain result could mean for themselves and their family members • Patient understanding the possibility of incidental findings unrelated to initial testing purpose • Patient awareness of the possibility of discordant findings (pathogenic variant identified in a gene that is inconsistent with the patient's personal and/or family history)
Insurance coverage and out-of-pocket costs 	• Patient is informed about potential out-of-pocket cost of genetic testing not covered by health insurance, which often ranges between $100 and $2000 depending on the insurance type and testing ordered • Patient awareness that subsequent genetic counseling and follow-up care may not be covered by health insurance

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Life insurance/disability/privacy concerns 	• Patient understands employment and insurance discrimination risks and protections • Patient can make informed decision about purchasing life insurance and understands life insurance and disability coverage is not protected by the Genetic Information Nondiscrimination Act (GINA) • Patient understands confidentiality considerations, including privacy, data security, and placement of results (ie, electronic health record) • Patient is aware of potential use of DNA sample(s) and data for future research
Results disclosure 	• Patient awareness of how and when they may receive their results, which may depend on the results themselves • A disclosure/discussion plan can be put in place if results are potentially complex
Potential results and possibility of VUS 	• Patient awareness of the difference between "positive" and "negative" results, which can have different meanings than other areas of medicine • Patient has general understanding of pathogenic, likely pathogenic, uncertain significance, likely benign, and benign • Patient awareness that VUS may be uncovered, which may or may not have future implications. A plan for continual contact with the patient can be made to ease feelings of uncertainty

DNA=deoxyribonucleic acid; VUS=variant(s) of unknown significance; WGS=whole-genome sequencing; WES= whole-exome sequencing.

Established guidelines may help to determine if individuals are ideal candidates for genetic testing (**Figure 2**). These guidelines propose that genetic testing be offered when the following conditions apply:[12]

1. An individual has a personal or family history suggestive of a genetic syndrome.
2. The results of the test can be interpreted.
3. Testing will influence medical management.

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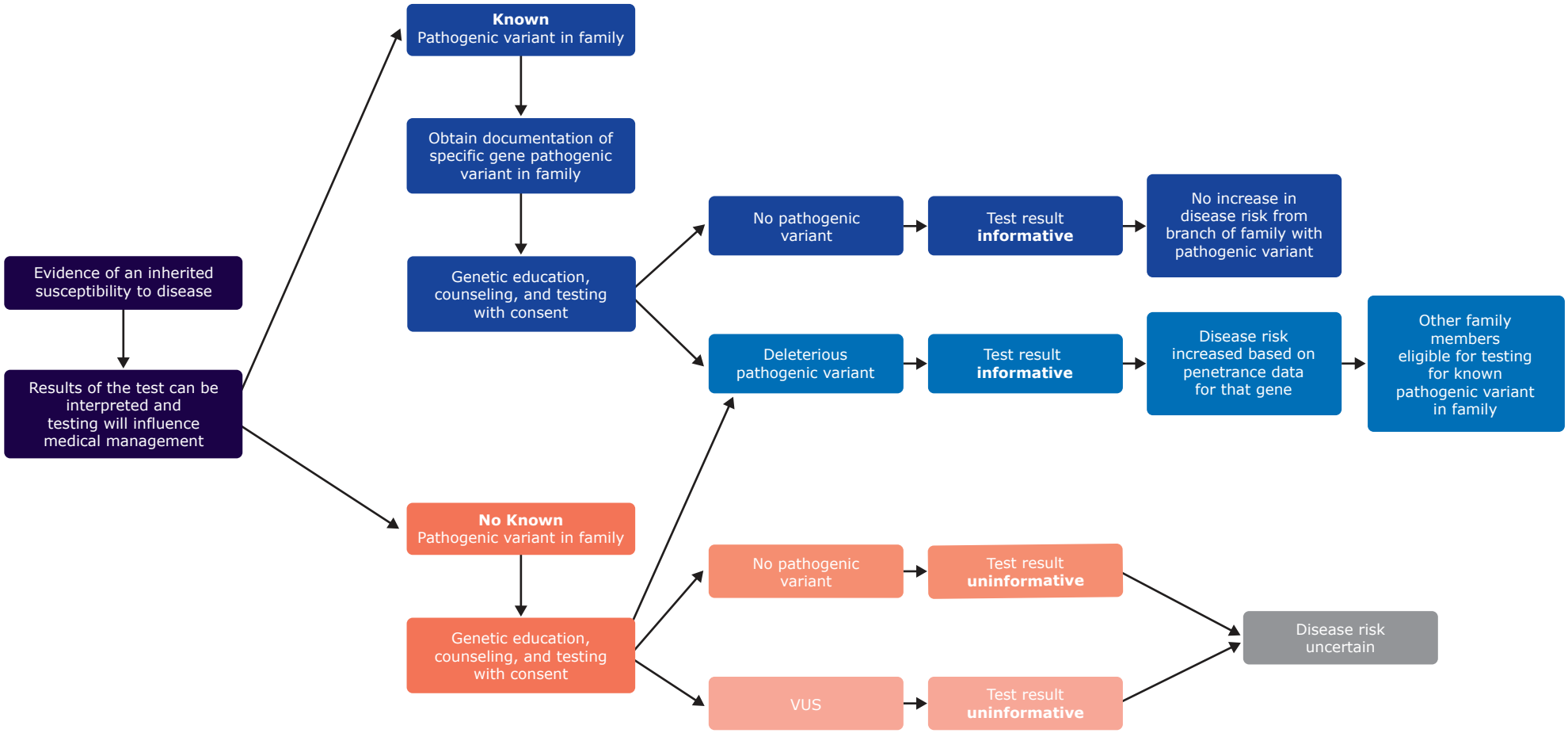
Beyond the discussion of potential test results, pre-test counseling often includes discussions about out-of-pocket costs and insurance coverage. Many advisors noted that insurance or Medicare restrictions represent key limitations for access to genetic testing. The overall cost to the patient may influence the kind of genetic testing ordered (eg, gene panel versus WES), the number of genes that can be ordered for a panel, and the facility where genetic testing can be performed. These restrictions may force providers to order sub-optimal testing at sub-optimal facilities.

Costs incurred by patients for genetic testing and follow-up care[8]

Although the cost of genetic testing has decreased rapidly over the past several decades, out-of-pocket costs can still present a barrier to those who may need genetic testing. Although insurance and Medicare may partially cover the costs of testing, out-of-pocket costs can often range from $100 to $2000. Beyond testing, insurance and Medicare may not cover the costs of follow-up care, including further genetic counseling or medical appointments and treatments.

FIGURE 2: GENETIC TESTING ALGORITHM FOR DISEASE SUSCEPTIBILITY[12]



VUS=variant(s) of unknown significance.

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Providers explained that pre-test counseling may include discussions about life insurance and/or disability. Advisors noted that HCPs who are not familiar with genetic testing may be unaware of the implications that testing can have on qualifying for life insurance or disability programs.

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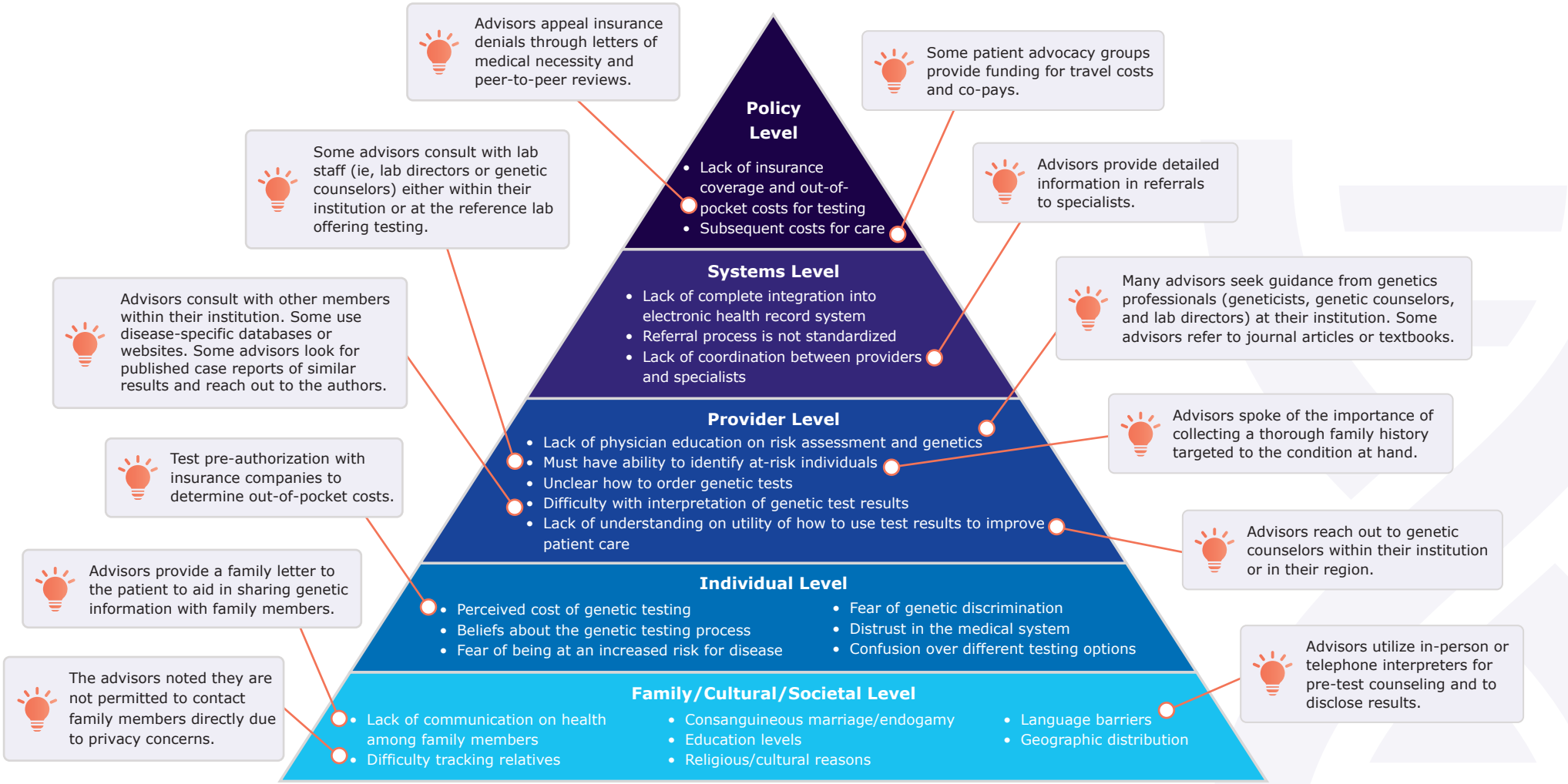
Barriers to Genetic Testing

Despite increasing availability and decreasing costs of genetic testing, several barriers remain in place that hinder patient access to this important healthcare resource. These barriers may exist at various levels throughout the genetic testing process, including at the patient, provider, clinic, insurance, and societal levels (**Figure 3**).[8]

FIGURE 3: BARRIERS ASSOCIATED WITH ACCESSING GENETIC TESTING AND POSSIBLE SOLUTIONS AND STRATEGIES[2,8-10,13-17]



EMR=electronic medical record; GC=genetic counselor.

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Advisors observed that families may feel hesitant about testing due to cultural and/or religious reasons. They cited the challenges of gaining trust from marginalized or minority populations, which is partially due to language barriers or lack of trust in the medical system. Furthermore, clinicians noted that in some cultures or religions, a particular pathogenic variant may negatively affect the patient's ability to get married as an adult.

Post-test Counseling

Following disclosure of genetic test results to a patient, that patient may or may not require post-test counseling. It is important that disclosure of genetic results is done in a way that is in the best interest of the patient.[9] Genetic results, whether positive or negative, may be a source of considerable anxiety for a patient. Some patients may need time to process results emotionally. Results revealing VUS may create confusion regarding how to proceed. All of these factors potentially create the need for multiple visits, allowing patients to consider their results and next steps.[10] Post-test counseling largely covers discussion around detected VUS, actionable test results, and coordination of future multi-disciplinary medical care (**Table 4**).[18]

TABLE 4: POST-TEST COUNSELING TOPICS AND IMPORTANCE[11,18]

Topic	Importance
Discussion of VUS	• Patient awareness that VUS may not be clinically actionable at the time but that this could change with future research • Patient understanding that VUS are not definitive indicators of disease
Actionable result	• Patient understanding of clinically significant results and what they mean in terms of prognosis, diagnosis, and disease risk • Understanding the disease, symptoms, and risk mitigation, if relevant • Patient awareness of how this impacts family members/offspring • Discuss methods for patients to communicate results to family members
Coordination of multi-disciplinary care	• Patient is made aware of options for further counseling and/or disease management • Awareness of treatment options, including psychological care, medical care, and support groups
Implications of genetic testing for family members	• Patient understanding of the pattern of variant transmission and risks of inheritance to children and other family members • Discuss the importance of sharing test results with family members

VUS=variant(s) of unknown significance.

Taking a Family History

Gathering a comprehensive and focused family history from patients with a confirmed or suspected genetic condition is important to inform recommendations about genetic testing for the patient and their relatives.[19] Family pedigree diagrams are a concise visual illustration of family structure and medical history. Analysis of family pedigree diagrams enable HCPs to infer the pattern of inheritance for Mendelian disorders and identify family members at risk.[20] HCPs are encouraged to construct family pedigree diagrams in a standardized format that denote sex and gender, deceased family members, and those who have been evaluated clinically and with genetic testing (along with the outcome).[13]

Pedigree analysis is a powerful tool when it is combined with genetic testing of at-risk family members, particularly for conditions that are managed more effectively in patients who are diagnosed early.[13] Fabry disease is a rare X-linked lysosomal storage disease for which early diagnosis improves monitoring and long-term management outcomes.[21,22] **Figure 4** shows a pedigree for a family with Fabry disease that was constructed through an investigation over several years and led to the diagnosis of several family members.[13]

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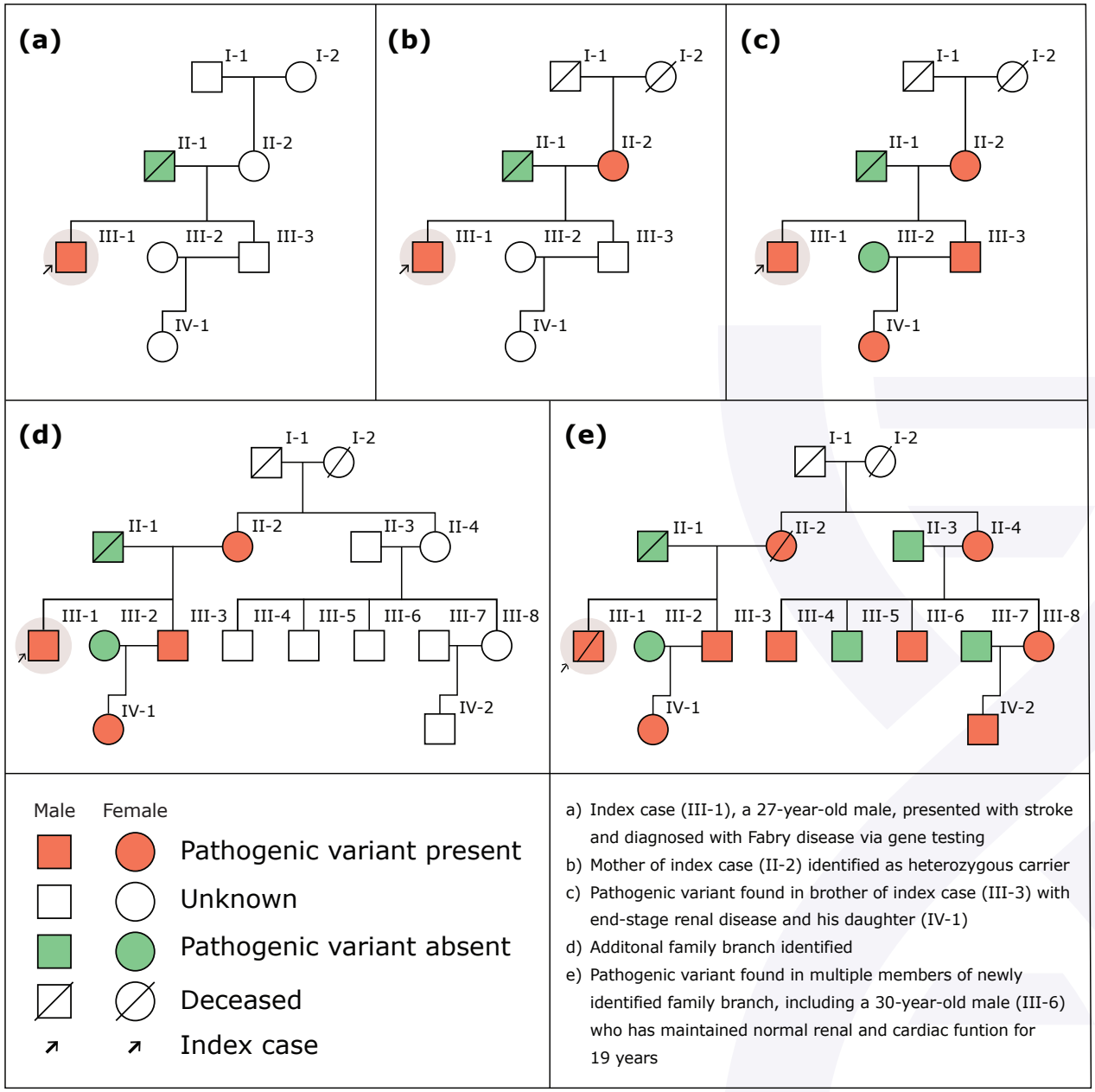
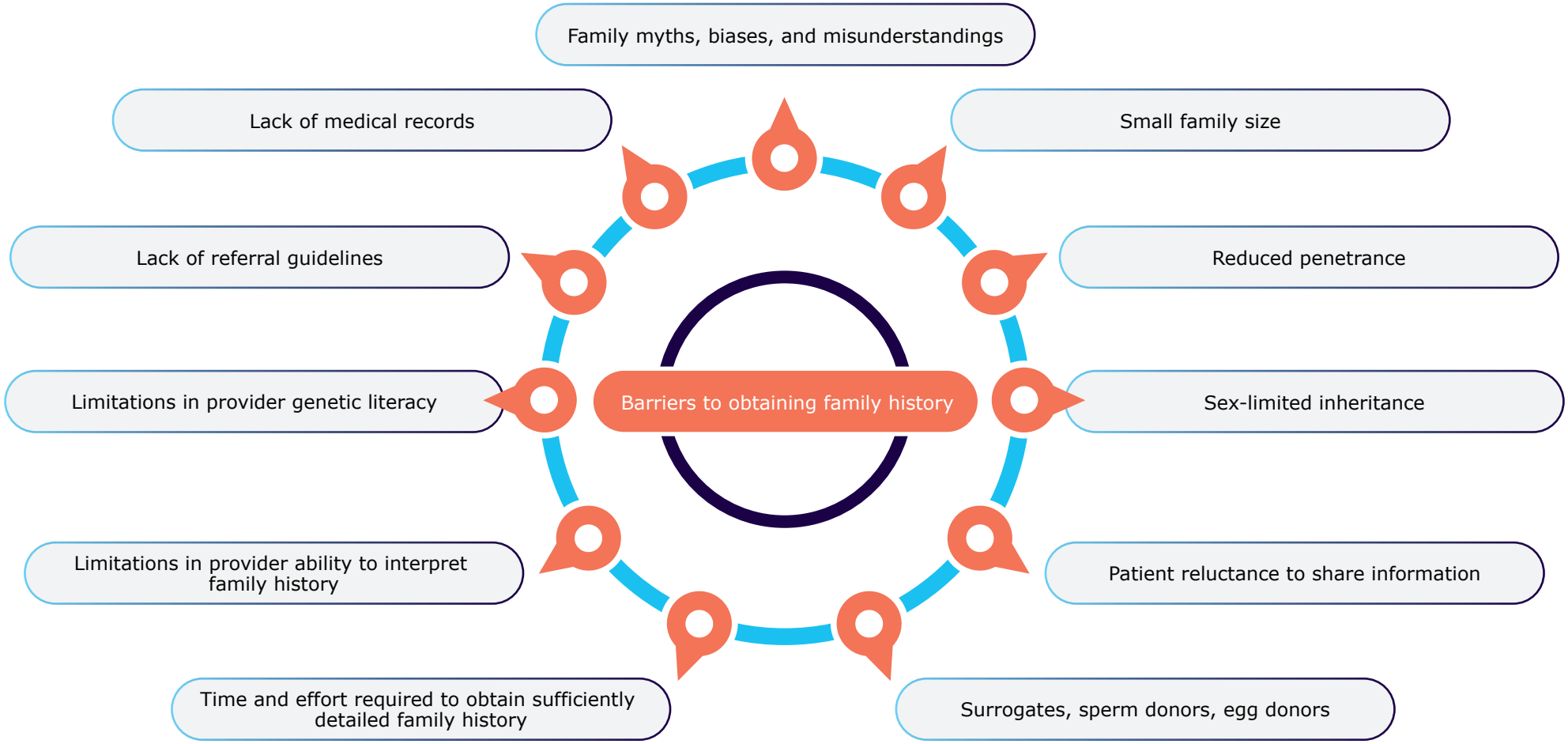
When gathering a family history, advisors explained that the number of generations they inquire about typically depends on the condition. Challenges in gathering a family history may include cases where the child or a parent is adopted, there is question of parentage, or when a gamete donor was used. Additionally, patients may not think of health problems their relatives have experienced or may not divulge them because they believe the symptoms are not relevant.

FIGURE 4: EXAMPLE OF EVOLUTION OF A PEDIGREE FOR A FAMILY WITH FABRY DISEASE[13]



Through the analysis of family pedigrees, HCPs may encounter "red flags" that point to increased genetic risk in a person or their family. The clearest red flag is the occurrence of the same or similar disorder in two or more relatives, particularly for rare and/or Mendelian conditions. Atypical features of disease presentation may also alert HCPs to important genetic factors, such as the age at onset being earlier than is typical for the disease or that the disease is present in the less commonly affected sex.[20,23] Other genetic red flags include multifocal disease (eg, bilateral retinoblastoma) and conditions known to be more common in certain ethnic groups (eg, Gaucher disease type 1 in Ashkenazi Jewish community).[20,23-25] Barriers to obtaining a family history are shown in **Figure 5**.

FIGURE 5: BARRIERS TO OBTAINING A FAMILY HISTORY[20,23,26]



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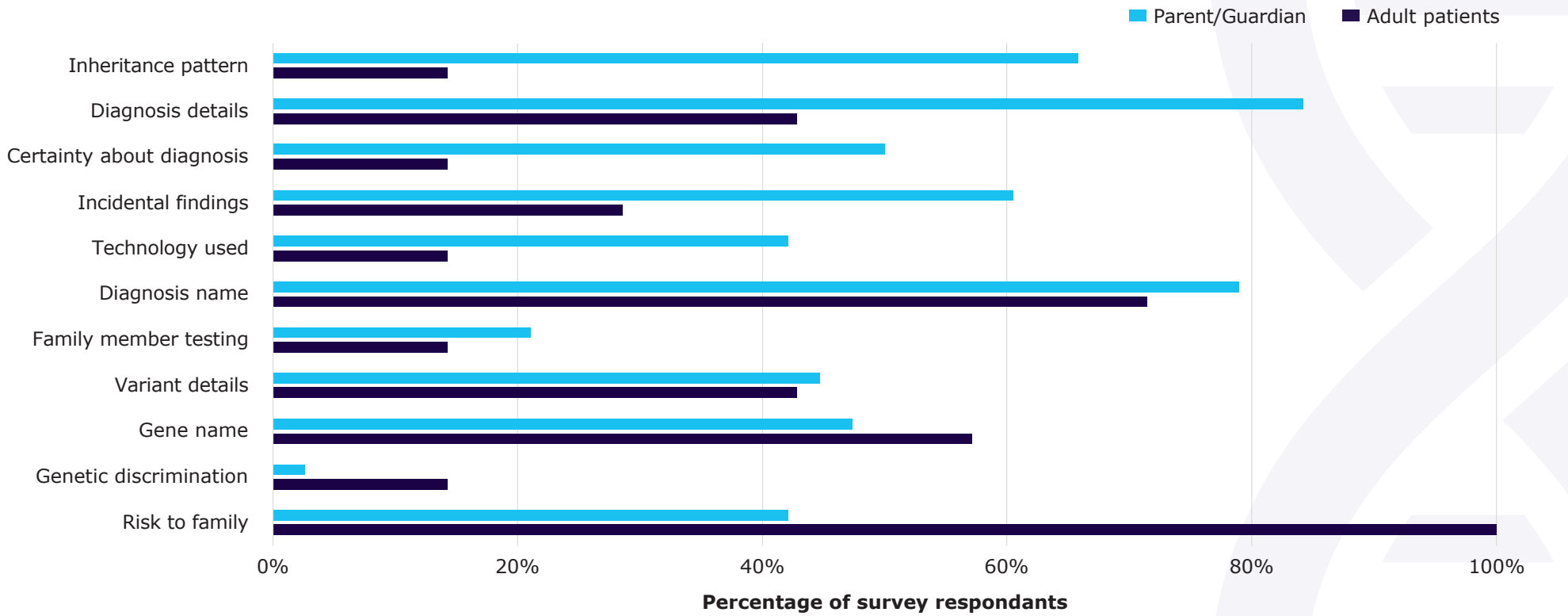
Family Implications in Genetic Testing

The implications of genetic test results extend to the family members of patients. Although communication of genetic test results with at-risk family members is considered the responsibility of the patient or their parents/guardians, HCPs can play a supporting role and should therefore be knowledgeable about the factors that influence a person's decision whether to share this information.[27,28] Communication with family members regarding genetic risk may be influenced by family structure, dynamics, and cultural practices within that family.[28]

For rare and undiagnosed conditions, the motivations to communicate genetic test results to family members are different for adult patients and parents/guardians of pediatric patients. Adult patients are more likely to be influenced by the potential health implications for family members, and parents/guardians are more likely to be influenced by details about the diagnosis and inheritance pattern (**Figure 6**).[27]

Beyond the complexities of family relationships, some patients may not feel comfortable sharing their results with family members due to the scientific nature of the results. Patient may feel the need to have their claims supported by a medical professional. Additionally, some patients fear not being believed by family members if the communication does not come directly from a medical professional. In this case, they may opt to bring family members to an appointment with a genetic counselor or specialist, or in some cases, request a letter explaining the genetic results on their behalf.[28]

FIGURE 6: FACTORS INFLUENCING THE DECISION TO SHARE GENETIC TEST RESULTS DIFFER FOR ADULTS AND PARENTS/GUARDIANS OF CHILDREN WITH RARE AND UNDIAGNOSED CONDITIONS[27]



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Advisors explained that at-risk family members may not always be available due to living in a different state or country, unknown parentage, incarceration, or various other circumstances. In these cases, advisors noted that they may try to provide letters and contact information that can be delivered to family members or their primary care providers. Letters may encourage family members to reach out regarding genetic testing.

Resources

Resource	Description	Visit
National Society of Genetic Counselors (NSGC) – Find a Genetic Counselor	The Find a Genetic Counselor directory offers access to over 3300 genetic counselors (US and Canada). The NSGC Find A Counselor directory is not a referral service, but, rather, a service to provide an up-to-date list of NSGC members.	https://findageneticcounselor.nsgc.org
NSGC Resources	The NSGC has put together a wide variety of resources, created and vetted by genetic counselors, to help support patients and provide more information on genetic counseling and genetic testing. Their resource library includes white papers, infographics, blog posts, podcast episodes, handouts and more.	https://www.aboutgeneticcounselors.org
National Library of Medicine	National Institutes of Health-supported genetic testing registry that acts as central location for genetic test information; includes each test's purpose, methodology, validity, and laboratory contacts	www.ncbi.nlm.nih.gov/gtr
National Organization for Rare Diseases	Dedicated to helping people with rare orphan diseases and assisting the organizations that serve them	www.rarediseases.org
Genetic Test Registry	Central location for voluntary submission of genetic test information (purpose, methodology, validity, evidence of the test's usefulness, and laboratory contacts and credentials) to advance the public health and research into the genetic basis of health and disease	https://www.ncbi.nlm.nih.gov/gtr
National Institutes of Health	Comprehensive information on health issues and clinical trials for HCPs and patients	www.nih.gov
ClinicalTrials.gov	Search engine for finding clinical trials	www.clinicaltrials.gov

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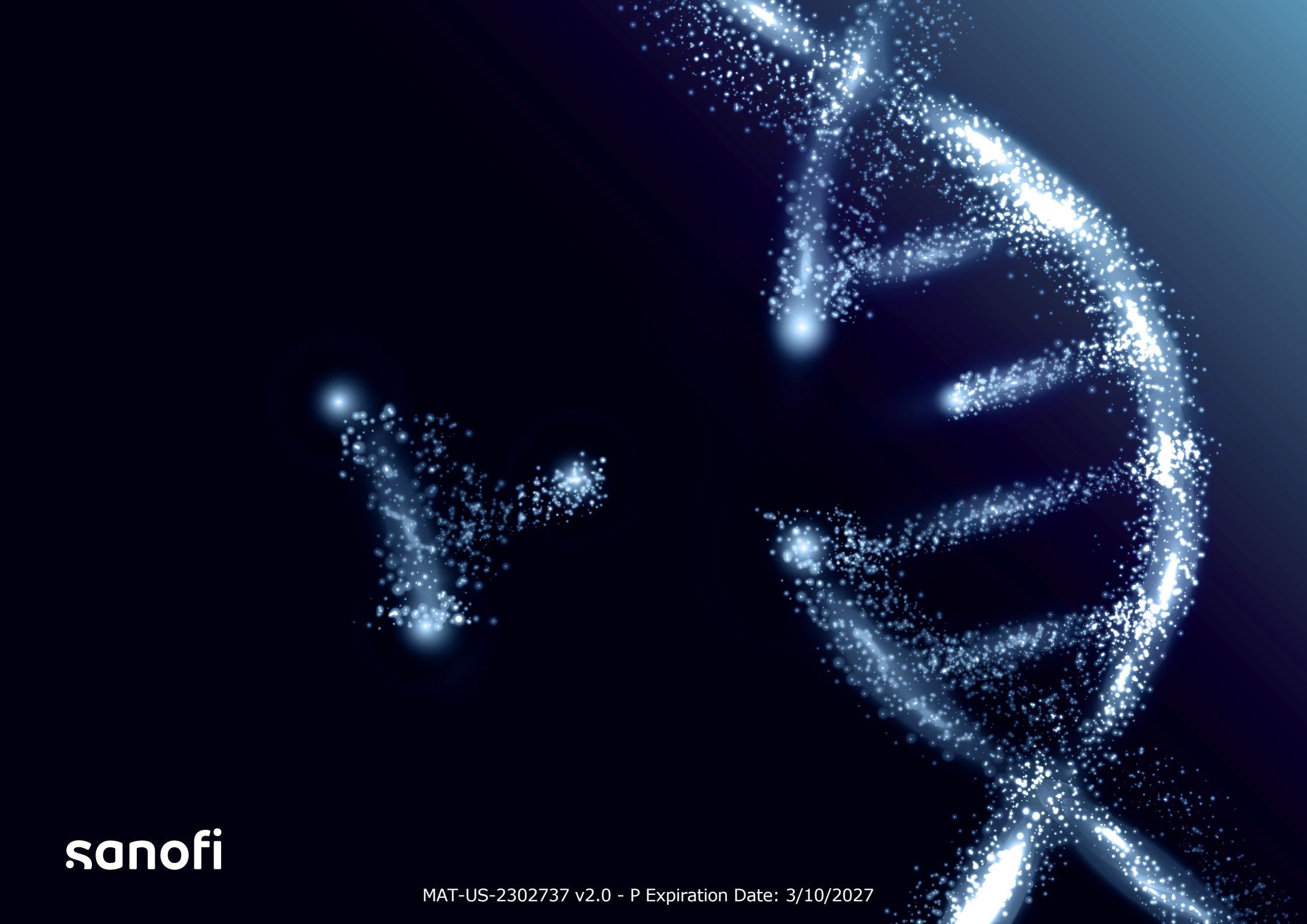

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