Solving Complex Hematology Challenges through Collaborative Genetic Counseling

Genetic counselors (GCs) play a critical role in healthcare for patients seeking information about how inherited and genetic disorders may affect them and their families. The role of a genetic counselor varies by organization, but the core responsibilities of this position often include assessing a patient's personal and family medical history, evaluating appropriate genetic testing options, interpreting test results, and empowering patients and their families with critical healthcare information.

Genetic counseling is a valuable service for patients with many different clinical indications, including personal or family histories of bleeding and clotting disorders. While testing is widely available through different laboratories, not all genetic testing services are created equal.

Overview of Genetic Counseling

First established as a formal clinical service in 1947, genetic counseling has evolved beyond its initial focus in reproductive medicine. Genetic counseling practice has been influenced by a variety of social, cultural, historical, loco-regional and technical factors. In turn, the goals and scope of genetic counseling have evolved (Resta, 2006). Today, genetic counselors practice in a wide variety of roles across the clinical spectrum including areas such as oncology, cardiology, neurology and other non-reproductive specialties.

Genetic counselors are typically lab-based or clinic-based, although they are not limited to those settings. The fundamental role of clinical genetic counselors is to work directly with patients to procure and interpret family and medical histories; identify at-risk individuals; explain genetics, inheritance and natural history; quantify chance of occurrence and recurrence; review available testing options; and facilitate decision-making regarding prevention and management. Laboratory genetic counselors support clinicians in navigating genetic testing options and integrating results into patient care. They also assess clinical information to guide laboratory staff in the prioritization of urgent samples and utilize knowledge of medical and family history, natural history and inheritance patterns to inform variant interpretation and generate meaningful clinical reports (Scacheri et al. 2008). Lab-based genetic counselors often center their practice around laboratory stewardship with the common goals of avoiding unnecessary testing, ensuring the most appropriate test is ordered, and reducing overall financial liability for each patient.

The Advantage of Expertise

Versiti's genetic counselors who work within our hematology genetics laboratory offer a distinct advantage in the identification of bleeding and clotting disorders, something few other laboratories provide. Our team's clinical domain expertise, honed through education, training, and clinical and laboratory experience, is recognized and reflected in numerous publications, national awards and participation on ClinGen Expert Panels, national and international panels, and committees of leading hematology organizations.

Whereas other genetic testing laboratories may offer testing options in an extensive number of specialties, every diagnostic panel in Versiti's test menu is specifically designed for hematology diagnosis, with careful gene-by-gene selection for clinical validity and utility, and comprehensive coverage of all tested regions. By

comparison, panels built upon an exome or genome platform analyze data across the entire set of human genes and scale back data analysis to cover only designated genes. In this approach, breadth is offered at the expense of depth, potentially resulting in gaps in coverage of relevant nucleotides, exons or genes.

Support for interpretation of individual results in the context of a given patient's clinical presentation is not guaranteed from every laboratory. Research has shown that many healthcare providers are not familiar with genetic testing procedures or test interpretation and lack confidence in providing genetics-informed care and discussing genomics and genetics topics with their patients (Schaibley et al. 2022). Additionally, a recent qualitative study assessing the genetic testing practices of physicians through focus groups noted that, "Most of the physicians wanted geneticists to be more involved in providing information and returning results" (Pasquier et al. 2021). All testing performed by Versiti's hematology genetics team includes genetics support, aiding providers in the interpretation of complex genetic results.

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Because of our deep expertise and specific focus in benign hematology, our genetic counselors maintain close relationships with the hematologists and hemophilia treatment centers (HTCs) across the country that serve a high concentration of patients with inherited hematological conditions. These connections ultimately benefit the patient, resulting in a familiar and collaborative approach to patient care. Our genetic counselors are always available for clinical consultation and, as part of testing protocol, our multidisciplinary team actively reviews patients' clinical history, contacts providers with clarifying questions as necessary, and works with clinicians to optimize orders as appropriate.

Genetic Counselors as an Extension of Your Team

Versiti's hematology genetics lab offers its clients a unique approach to genetic diagnosis and disease identification utilizing a multidisciplinary team, that includes genetic counselors with deep, focused expertise in non-malignant hematology. Our GCs act as an extension of the patient's medical team, providing both consultation for test selection as well as detailed, interpretive reporting of results. Because our program is centered around benign hematological disorders, our GC team has a deep understanding of specific disease states and the genes and variants that cause them.

For example, a recent case reviewed by the Versiti hematology genetics team involved a 4-month-old male with severe hemophilia B. He was referred to Versiti for genetic testing after being admitted at 2 weeks of age with prolonged bleeding following circumcision, which led to discovery of a factor IX activity of less than 1%. This patient had no known family history of bleeding disorders; genetic analysis of *F9* by NGS with reflex to deletion/duplication analysis by array comparative genomic hybridization (aCGH) was ordered. The finding of the hemizygous pathogenic variant (*F9* c.-35G>A) was identified by NGS, eliminating the need for reflexive aCGH testing. Furthermore, with the coagulation expertise of the Versiti hematology genetics team, the significance of this specific variant causing the rare subtype of hemophilia B Leyden was recognized in the variant interpretation and emphasized in the patient-specific summary and recommendation in the results report. Hemophilia B Leyden results from specific variants in the *F9* promoter region (5' untranslated region) and is characterized by improvement of the factor IX activity with age. Unlike typical hemophilia B, those with the Leyden subtype typically "outgrow" hemophilia with factor IX levels in the normal or low-normal range by early adulthood. In the patient's results report, our team recommended monitoring the patient's baseline factor IX activity as he ages, including periodic assessment of washout samples without residual factor IX from treatment, to assist with medical management decisions over time. Without genetic analysis and identification of this particular pathogenic variant, this patient may have continued to prophylactically receive factor IX replacement therapy unnecessarily throughout his life.

In addition to Versiti's hematology genetics lab approach to case management, our multi-disciplinary team of benign hematology experts works collaboratively across the clinic and laboratory settings to solve complex patient cases, providing actionable diagnostic results. One such example is that of a 68-year-old female diagnosed with immune thrombocytopenic purpura (ITP) from the age of 15 who was referred to Versiti with a concern for congenital thrombocytopenia following a recent retinal hemorrhage.

Over the patient's lifetime, she had not responded to steroids, intravenous immunoglobulin, eltrombopag, fostamatinib or rituximab, nor did she have a family history of thrombocytopenia. Mean platelet volumes were within reference ranges and a bone marrow biopsy showed normal cellularity with trilineage hematopoiesis and mild megakaryocytic hyperplasia with a subset of dysmegakaryopoiesis present, which was reported to be concerning for myelodysplastic syndrome (MDS) with single lineage dysplasia. Platelet autoantibody testing performed in Versiti's platelet and neutrophil immunology laboratory was positive for autoreactive antibodies directed at platelet glycoproteins. Testing with the inherited thrombocytopenia panel by NGS with reflex to deletion/duplication analysis by aCGH was requested.

The heterozygous pathogenic variant (*ANKRD26* c.-128C>T) was identified by NGS and is consistent with the diagnosis of *ANKRD26*-related thrombocytopenia; deletion/duplication analysis via aCGH was not performed due to the findings via NGS. As this condition carries a risk of transformation to a myeloid neoplasm, our reporting included a recommendation for evaluation at a center with experience in germline syndromes with predisposition to hematologic malignancy for formulation of a surveillance plan. Genetic evaluation and results interpretation by Versiti's multidisciplinary team identified a pathogenic variant that confirmed a specific diagnosis of inherited thrombocytopenia, generated recommendations for appropriate surveillance, and advised against any further unneeded therapy after years of treatment for ITP.

Our commitment to laboratory stewardship is integrated into every aspect of our hematology genetics service. When reviewing test orders, our staff carefully evaluates the patient's clinical information and family history to determine if the requested diagnostic test or panel is the optimal choice to address the clinical concern without introducing unnecessary likelihood of off-target findings, including variants of uncertain significance. For example, an 18-month-old female was referred to Versiti's hematology genetics lab with a suspected platelet function disorder after experiencing significant epistaxis since the age of 8 months old. The patient's provider was able to exclude many disorders diagnosed by Versiti's platelet function disorder panel by way of previous functional studies performed and wanted to optimize the patient's genetic testing by utilizing a custom blood disorder panel. In collaboration with Versiti's hematologists and genetic counselors, a suggested custom panel was ordered that included genes *ANO6, P2RY12, PLA2G4A, RASGRP2, RUNX1* and *TBXA2R*. Testing revealed the presence of one likely pathogenic variant (*RASGRP2* c.1096-1G>A) and one variant of unknown significance (VUS). Following these results, targeted parental studies were performed, leading to a reclassification of the VUS (*RASGRP2* c.146C>T, p.Ser49Phe) as a likely pathogenic variant based on additional evidence of *de novo* occurrence. Thoughtful collaboration between the patient's provider and Versiti's hematology genetics team allowed for informed gene selection, identification of a new likely pathogenic variant, and ultimately a precise diagnosis that resulted in optimized patient care.

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Conclusion

When considering genetic testing for patients with known or suspected hematological disorders, selection of the performing laboratory is critical for accurate diagnosis and invaluable support. Versiti's hematology genetics team offers comprehensive testing services with domain-specific expertise and a dedication to laboratory stewardship, reducing the financial liability for your patients. Genetic testing performed at Versiti

delivers patients and providers a unique advantage with individualized, meaningful reports to support informed decision making and provide actionable diagnostic information. For more information about Versiti's hematology genetics testing, visit Versiti.org/HG.

Sources

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