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Stagnation in quality of next-generation sequencing assays for the diagnosis of hereditary hematopoietic malignancies

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Abstract

Hereditary hematopoietic malignancies (HHMs) are inherited syndromes that confer the risk of blood cancer development. With the rapid acceleration of next-generation sequencing (NGS) into commercial biotechnology markets, HHMs are increasingly recognized by genetic counselors and clinicians. In 2020, it was demonstrated that most diagnostic test offerings for HHMs were insufficient for accurate diagnosis, failing to sequence the full spectrum of genetic events known to cause HHMs. We hypothesized the number of genes on commercially available HHM assay increased from 2020 to 2022, consistent with a more comprehensive sequencing approach. Here, we analyzed assays from eight commercial laboratories to determine the HHM-related genes sequenced by these assays. We compared these assays with panels from 2020 to determine trends in sequencing quality. Most HHM diagnostic assays did not change and remain insensitive for the detection of all HHM-related variants. Most (75%) HHM assays do not sequence *CHEK2*, the gene most frequently mutated in HHMs, and 25% of HHM assays does not sequence *DDX41*, the second most frequent HHM driver. The quality of HHM diagnostic assays stagnated despite the discovery of novel HHM-related genes and prior work demonstrating heterogeneity in the quality of HHM testing. Most commercially available HHM tests remain insufficient.

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AUTHOR CONTRIBUTIONS

G.W.R. contributed to the design of the study, performed data collection, performed data analysis, and drafted the manuscript. R.S. performed data collection and data analysis, and contributed to the manuscript. T.E.O. performed data collection and contributed to the manuscript. G.A.H. conceived and designed the study, supervised data analysis, and contributed to the manuscript. All authors have approved the final manuscript. G.W.R., R.S., T.E.O., F.H., and M.W.D. confirm that they had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors gave final approval of this version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

HUMAN STUDIES AND INFORMED CONSENT

No human studies were performed for the work presented in this manuscript.

ANIMAL STUDIES

No non-human studies were performed for the work presented in this manuscript.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

CONFLICT OF INTEREST

M.W.D. serves on the Scientific Advisory Board for Argenx. The remaining authors declare no conflicts of interest.

Keywords

cancer risk; clinical cancer genetics; germline genetics; hereditary hematopoietic malignancies; hereditary leukemia; inherited leukemia; next-generation sequencing

Genetic counselors have traditionally been the health care providers responsible for the ordering of genetic tests, but the number of other health care providers who now order and interpret genetic tests has increased exponentially as the availability of genetic testing has increased over the past decade (George et al., 2016; Rahman, 2014; Valencia et al., 2017). These other health care providers, with little to no genetics training, often rely on the laboratory themselves to provide the most up-to-date, scientifically sound assays (Farmer et al., 2021; Ramos & Weissman, 2018).

Hereditary hematopoietic malignancies (HHMs) are hereditary blood cancer syndromes driven by germline pathogenic/likely pathogenic (P/LP) variants. Although research regarding HHMs is relatively new, all HHMs to date have followed Mendelian inheritance patterns (Roloff, Drazer, et al., 2021). The scientific basis and clinical recognition of HHMs have increased with the rapid uptake of next-generation sequencing (NGS) in research and clinical settings. The process of confirming germline variants in HHMs requires multiple diagnostic steps, as peripheral blood represents tumor tissue that carries both germline and somatic alterations. Although germline variants can be incidentally detected via tumor-only sequencing panels (Drazer et al., 2018), the gold standard for identifying a germline variant in a patient with an active hematopoietic malignancy is sequencing DNA from cultured skin fibroblasts (Kraft & Godley, 2020).

The accurate diagnosis of an HHM also requires NGS panels that sequence the full spectrum of genes involved in HHMs and sequencing techniques that are capable of detecting the various types of variants that drive HHMs (i.e., single nucleotide variants, insertions/deletions, and structural events such as copy number changes). The number of HHM-related genes, however, has rapidly increased as the genetic basis of HHMs continues to be elucidated (Tawana et al., 2022). This requires HHM diagnostic assays to be updated frequently in response to advances in scientific knowledge. One unique problem in the HHM field, however, is that the quality of HHM diagnostic assays is highly variable (Roloff, Godley, et al., 2021). Most HHM assays used in 2020, for example, did not sequence all research-identified HHM-related genes. These omissions increase the risk of false-negative test results. Specific to HHM patients, this omission leaves them vulnerable to a treatment-related second malignancy, such as a donor-derived leukemia. A donor-derived leukemia occurs when stem cells from a matched related donor, who unknowingly carries an HHM-related genetic mutation, are provided to an affected recipient. Other concerns, shared with solid-tumor hereditary cancers, include missed opportunities for additional cancer screenings (some HHMs also carry an increased risk for solid tumors) and reduce opportunities for cascade testing of family members (who may benefit from genetic counseling and personalized cancer screening). In addition, other HHM assays in 2020 accepted DNA from peripheral blood mononuclear cells, as a permissible tissue source in HHM patients. Sequencing DNA from peripheral blood in patients with active hematopoietic

malignancies increases the risk for false-positive HHM test results, as NGS assays may detect both somatic variants in residual tumor tissue and/or clonal hematopoiesis-related variants (Churpek et al., 2015; DiFilippo et al., 2020; Drazer et al., 2018, 2022; McReynolds et al., 2019).

It is unclear how the landscape of HHM diagnostic testing has changed since we performed our original analysis of commercial testing practices in 2020 (Roloff, Godley, et al., 2021). We identified all commercial diagnostic companies available in the United States that offered NGS panels intended for HHM diagnosis in January 2022 to investigate which laboratories have updated their assays. We analyzed the spectrum of HHM-related genes sequenced by each commercial panel and compared these genes with prior offerings from the same company. Here, we demonstrate that the quality of commercial HHM test offerings has largely stagnated since 2020, despite growing recognition of these hereditary blood syndromes and prior work demonstrating the low quality of HHM diagnostic assays.

We identified HHM assays offered by commercial laboratories that we analyzed in our previous report. In addition, we queried the US National Center for Biotechnology Information's Genetic Testing Registry to identify all newly offered HHM test offerings since our original analysis. The updated analysis was performed in January 2022, 1 year after the print publication and 16 months after the e-publication of our prior study (Roloff, Godley, et al., 2021). We focused our analysis on NGS panels for the diagnosis of hereditary myelodysplastic syndrome and hereditary leukemia.

We evaluated all genes on HHM-related panels via a binary matrix approach. We calculated the proportion of panels that sequenced each HHM gene of interest and queried the Online Mendelian Inheritance in Man catalog to confirm the association of each HHM-related gene and a relevant HHM phenotype (Table S1). Our analysis also included HHM-related genes that were most commonly mutated in a recent series of unselected patients with acute myeloid leukemia (Table S1; Yang et al., 2022). The most frequently sequenced genes across HHM panels for 2020 and 2022 are plotted in Figure 1, defining a core set of HHM genes that were analyzed by the majority of commercial assays. We also plotted the proportion of HHM panels that sequenced a gene of interest in 2020 and 2022 to identify trends in gene-specific sequencing during this time period (Figure 2, Figure S1).

We analyzed HHM panels from eight companies (Figure 1). Only four genes (*CEBPA*, *GATA2*, *RUNX1*, *TP53*) were sequenced by all eight panels. An additional 25 genes were sequenced on 50% or more of the panels. Only 25% of HHM panels sequenced *CHEK2*. Variants in *CHEK2* have been known to be associated with lymphoid malignancies since the 2000s, and *CHEK2* variants were the most common germline drivers observed in a recent series of patients with myeloid malignancies (Cybulski et al., 2004; Rudd et al., 2006; Yang et al., 2022). *CHEK2* was also mutated in the germline of a patient who developed a therapy-related myeloid neoplasm after receiving radiation monotherapy (Patel et al., 2021) as well as in two patients who carried pathogenic/likely pathogenic variants that they shared with their matched related donors during stem cell transplant (Feurstein et al., 2022). Given the important and evolving role of germline *CHEK2* variants in both lymphoid and myeloid

blood cancers, we anticipate that sequencing of *CHEK2* will increase during the upcoming years.

Only 75% of HHM panels sequenced *DDX41*, which was previously considered the gene that is most commonly altered in HHMs (Polprasert et al., 2015). The discordance between the noted prevalence of variants in HHM-associated genes in Yang et al. (2022) and their inclusion on commercial HHM panels is depicted in Figure S2. Several important HHM genes such as *BRCA1* and *BRCA2*, which are known to be enriched for germline variants within the therapy-related myeloid neoplasm population (Churpek et al., 2016; Martin et al., 2009; McNerney et al., 2017; Schulz et al., 2012), appeared on only a minority of panels (Figure 1). Similarly, *CSF3R*, *FANCA*, and *MBD4* were sequenced only by a minority of panels despite known roles in HHMs (Roloff, Godley, et al., 2021). By contrast, *EPCAM*, which is not implicated in the etiology or pathogenesis of any known HHM, was present on half of all panels.

Trends in the analysis of the 25 most-analyzed HHM-related genes from 2020 to January 2022 are shown in Figure 2. Most HHM assays that previously omitted critical HHM genes made no changes to their panels over this time period. This stagnancy persisted despite multiple associations between candidate genes and HHM phenotypes in public databases (Figure S2). Only one laboratory made significant changes to their panel by adding eight HHM-related genes (*ANKRD26*, *CBL*, *DDX41*, *ETV6*, *PTPN11*, *SAMD9*, *SAMD9L*, *SRP72*; Figure S1). As in our original study, the criteria used to include and/or exclude genes from HHM-sequencing assays were largely not published on patient and/or provider-facing resources. No major changes in sequencing methodology had occurred since the time of our initial publication. Similarly, we once again observed that many laboratories did not accept germline tissue specimens, such as cultured skin fibroblasts, that are necessary to perform germline sequencing in patients with active blood cancers (Roloff, Godley, et al., 2021).

The accurate diagnosis of an HHM guides patient care in several clinically meaningful ways. First, the identification of an HHM variant informs genetic counseling for the affected patient, while also streamlining cascade genetic testing for both affected and unaffected family members (University of Chicago Hematopoietic Malignancies Cancer Risk Team, 2016). Additionally, the identification of an HHM P/LP variant refines the stem cell transplant process by allowing physicians to avoid using unaffected related variant carriers as stem cell donors. This approach reduces the likelihood of donor-derived malignancies while also avoiding the currently unknown risks associated with the use of hematopoietic growth factors for stem cell mobilization in HHM P/LP variant carriers (Kobayashi et al., 2017). Finally, the identification of an HHM-related variants may also guide therapeutic decision-making. Recent evidence, for example, supports the utilization of lenalidomide for patients with myeloid malignancies driven by P/LP germline *DDX41* variants even in the absence of the recurrent del(5q) abnormality (Abou Dalle et al., 2020; Negoro et al., 2016).

Here, we provide further evidence that the majority of HHM diagnostic assays remain inadequate for the accuracy of diagnosis of these syndromes. Stagnation in the quality of HHM diagnostic assays has occurred despite the discovery of novel HHM-related genes,

the publication of society-level guidelines including recommendations on HHM testing (Arber et al., 2022; Döhner et al., 2022), as well as the publication of our initial study in January 2021. Four genes (*CEBPA*, *GATA2*, *RUNX1*, and *TP53*) were uniformly sequenced, likely because the role of these genes in HHMs is well-characterized. However, P/LP germline variants in these genes are now known to be relatively infrequent as compared to variants in genes such as *CHEK2* and *DDX41* (Feurstein et al., 2022; Yang et al., 2022). This demonstrates that contemporary HHM diagnostic panels must be updated to reflect developments in the field. In order to reduce the risk of false-negative diagnostic reports, the quality of HHM diagnostic testing must be improved so that the most common drivers of HHMs, such as *CHEK2* and *DDX41*, as well as highly penetrant, but less common, HHMs, such as *ETV6*, *GATA2*, and *RUNX1*, are universally sequenced and analyzed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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What is known about this topic

Most commercially available tests assessing inherited blood cancer risk are not sufficiently comprehensive. Stewardship of commercial testing has become a responsibility largely assumed by genetic counselors.

What this paper adds to the topic

This study systematically appraises the evolution of diagnostic tests for hereditary hematopoietic malignancies over time.

FIGURE 1.

Comprehensive analysis of hereditary hematopoietic malignancy diagnostic panels from eight commercial offerings. The heatmap depicts data via a binary matrix whereby any single gene included on one commercial panel is cross-referenced for inclusion on other assays analyzed. Genes are organized from left to right by decreasing proportion across all panels.

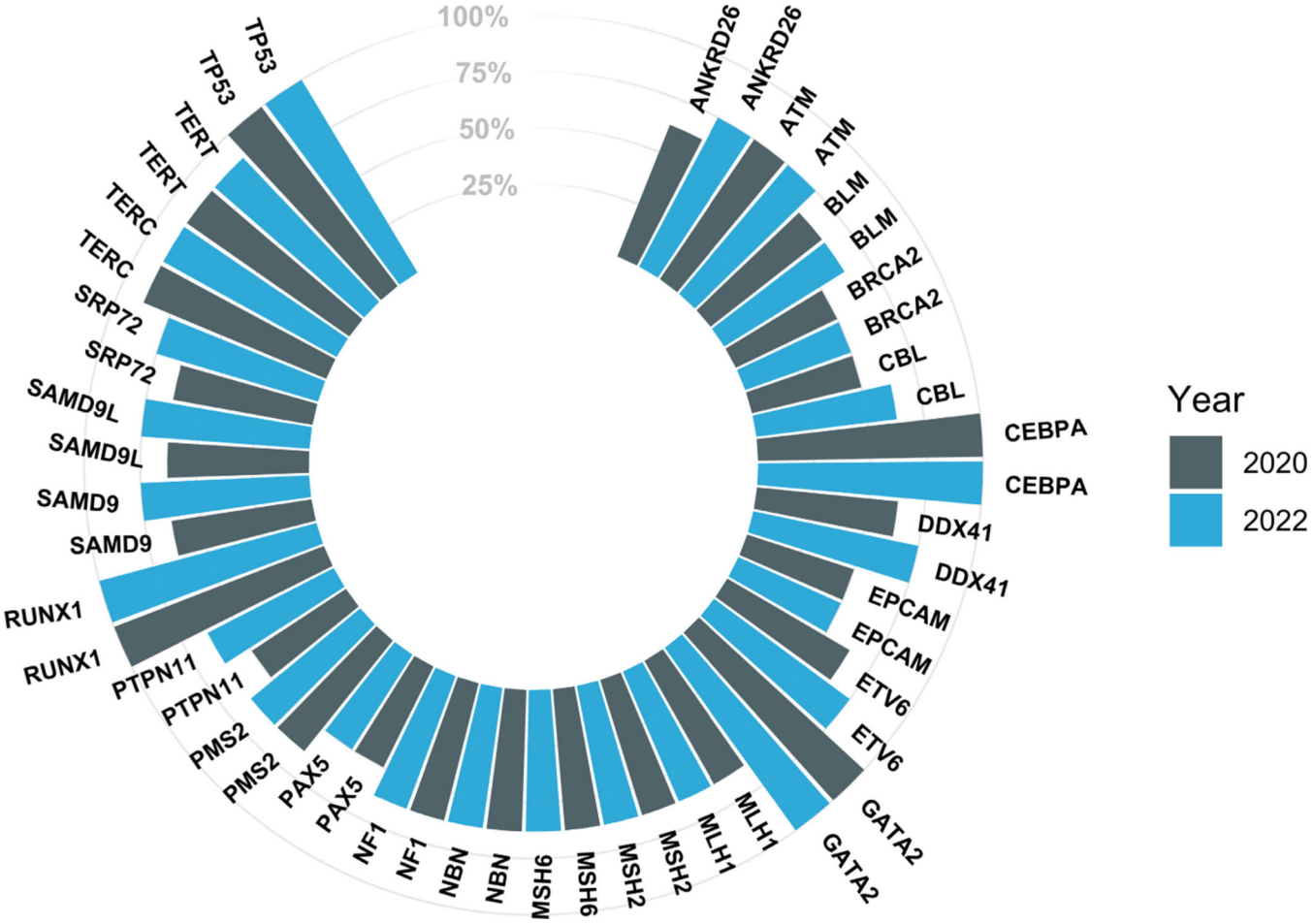

FIGURE 2.

Analysis of commercial assay gene composition over time. This plot demonstrates percent composition of commercial panel inclusion for genes implicated in hereditary hematopoietic malignancies (HHMs). To emphasize high-yield HHM genes, only those included on at least half (4/8) of panels are displayed. Genes are depicted in pairs, demonstrating longitudinal change by the year analyzed.