Historically, professional society guidelines have recommended limited genetic testing for hereditary cancer syndromes (HCS) to patients with cancer thought to be at highest risk for carrying pathogenic/likely pathogenic germline variants (PGVs) in a few selected genes. Reasons for this approach were largely based on the high costs of testing, perceptions that HCS were rare in the general population, and a paucity of clinical utility. Here, we discuss the current evidence that challenges these assumptions and supports the implementation of universal HCS testing among patients with solid tumors.

Numerous studies exploring PGV rates in unselected populations across various solid tumor types have been conducted to estimate HCS prevalence and risk. Contrary to initial perceptions, PGVs were found in a substantial proportion of patients with common solid tumors who were unselected for family history or other putative risk factors (3.9%-56.2%; Fig 1A and Data Supplement). Although compelling, these findings, with rare exception, have not been sufficient to change testing guidelines. Additional studies, initially limited to BRCA1 and BRCA2 in patients with breast cancer, investigated the clinical utility of identifying PGVs in HCS genes and demonstrated that genetic test results do, in fact, inform treatment, clinical trial enrollment, clinical management, and patient decisions. As additional studies demonstrated the value of testing for PGVs in more breast cancer genes, such as TP53, ATM, CHEK2, and PALB2, guidelines have evolved to recommend inclusion of these genes in multigene panel tests (MGPTs).

Similar observations expanding the range of impactful genes have been documented for other cancer types, such as ovarian, colorectal, and pancreatic cancers. These two sets of findings have led to incremental expansions of testing guidelines to include risk factors beyond family history and testing for genes beyond BRCA1 and BRCA2.

Germline testing guidelines for solid tumors have laid the foundation for medical coverage policies from health insurance payers specifying which patients are eligible for testing reimbursement and which genes should be included in testing. For example, both private payers and Medicare reference the National Comprehensive Cancer Network (NCCN) testing guidelines when providing eligibility criteria and dictating which genes should be assayed. Moreover, coverage policies on the basis of the guidelines vary among payers, making it difficult for clinicians to determine which of their patients are eligible for testing reimbursement or might require out-of-pocket payment. Although the overall eligibility set by each payer overlaps significantly, the explicit criteria vary widely. For example, both Anthem Blue Cross and United Healthcare require the validated BRCA1 and BRCA2 assessment tools to be used, but the allowed, proscribed tools do differ (although with some overlap). Medicare requires patients with a personal history of breast or ovarian cancer to meet NCCN criteria before meeting more stringent formal risk assessments. These policies also vary in which genes are covered for patients who meet eligibility criteria. For example, United Healthcare indicates that BRCA1, BRCA2, CDH1, PALB2, PTEN, and TP53 should be analyzed as high-penetrance breast cancer susceptibility genes, whereas Anthem Blue Cross and Medicare only have policies for BRCA1 and BRCA2 testing in patients with breast cancer. Furthermore, out-of-pocket costs for patients who would benefit from testing but are not covered by their insurance can result in patient payments upward of $250 US dollars, creating financial barriers that may render clinically indicated testing inaccessible. In fact, both clinicians and patients cite cost and insurance coverage as barriers to genetic testing for hereditary cancer.

For these reasons, a universal approach to MGPT for all patients with solid tumor cancer has the potential to lessen confusion about who is (or not) eligible for testing and who will (or not) have insurance coverage for testing, which ultimately has the potential to increase access to and reduce disparities in germline cancer genetic testing.
How many patients with cancer are we missing by applying restrictive testing guidelines? Studies across numerous cancer types have begun to address this question, and mounting evidence demonstrates that testing guidelines miss an unacceptable number of individuals with PGVs in HCS genes across many cancer types (Fig 1B and Data Supplement). The percentage of patients with a PGV was substantial among those not meeting testing criteria (although usually lower compared with patients who met criteria). More importantly, because the absolute number of patients not meeting testing criteria is usually much greater than the number meeting criteria, the total number of patients with a PGV is also greater among those who do not meet criteria. For example, before guidelines were recently updated, only patients with metastatic castration-resistant prostate cancer (mCRPC; approximately 10% of all prostate cancers) were eligible for germline genetic testing, with an estimated diagnostic yield of approximately 11% for homologous recombination repair gene defects. The remaining patients without mCRPC have an estimated 5% diagnostic yield. Among a group of 1,000 patients with prostate cancer, 11 of 100 patients with mCRPC and 42 of 900 patients with non-mCRPC (10 of 135 with higher risk localized; 21 of 765 others) would be expected to have a PGV in an HCS gene. Thus, 31 (74%) of the 42 patients with a homologous recombination defect were not being tested, and therefore, their PGVs would go undetected.

Failing to identify PGVs in HCS genes has clinical implications. Two recent pan-cancer studies assessing the performance of testing guidelines quantified the patients with PGVs that would have been missed, as well as the resultant changes to clinical management changes. Mandelker et al demonstrated that more than half of the patients with actionable PGVs (55%) would have failed to be tested under legacy genetic testing guidelines. The recent prospective, multisite Interrogating Cancer Etiology using Proactive genetic Testing (INTERCEPT) study found...
that clinicians caring for 42 (28.2%) of 149 patients with high-penetrance PGVs documented modifications to treatment and medical management as a result of the findings. These findings are also supported by other studies that have explored individual cancer types more deeply, including breast, colorectal, pancreatic, gastrointestinal, prostate, and other urogenital cancers.

Innovating Implementation Strategies

On the basis of evidence demonstrating the utility of universal germline genetic testing for pancreatic and ovarian cancers, guidelines from the NCCN have recommended testing for all patients diagnosed with these cancer types for several years. Guidelines for other cancer types are also evolving to liberalize inclusion criteria on the basis of current evidence. For example, a prospective cohort of patients with breast cancer found similar PGV rates in those who met and those who did not meet testing guidelines, leading the American Society of Breast Surgeons to recommend genetic testing for all patients with breast cancer.

Health insurance policies have expanded, with United Healthcare releasing a policy in January 2020 stating that germline MGPT is proven and medically necessary for all patients diagnosed with any Lynch syndrome–associated cancer. Medicare has also expanded coverage for MGPT. Health systems, such as Intermountain Health, have initiated programs that provide genetic testing to all patients with cancer. More recently, on the basis of the findings from the INTERCEPT study, the Mayo Clinic has begun to develop strategies for implementing universal germline genetic testing for their patients with cancer. However, large gaps in uniform payer policies remain, with some regions disallowing any MGPT, underscoring the importance of continuing to evaluate and quantify both the clinical benefits and cost-effectiveness of universal MGPT for all patients with solid tumors.

The growing body of evidence supporting universal testing has stimulated discussion of the related implementation challenges with current health care infrastructures. Although a valid concern, it may be unfounded. Despite clear testing guidelines for all patients with ovarian, pancreatic, and metastatic prostate cancers, underutilization of genetic testing persists with rates around approximately 30%, 38%, and approximately 10%. Similar utilization rates were also observed for other cancer types with well-defined guidelines, with only approximately 5% of eligible patients with colorectal cancer, approximately 25%-30% of eligible patients with breast cancer, and approximately 30% of eligible patients with prostate cancer with genetic testing ordered.

As genetic testing becomes integrated into the standard of care for patients with cancer, it is clear that the demand for genetic counselors and other specialists far exceeds the current supply. However, shifts in health care caused by COVID-19 disease have demonstrated that telehealth and other virtual approaches are an effective means to providing access to genetics care. Implementation of streamlined processes can help mitigate logistical challenges; for example, automated referrals for pancreatic cancer have increased testing uptake while minimizing workflow interruptions. Another innovative approach is the implementation of software that performs human-like conversations with users via text messages (chatbot) to initiate the genetic testing process, collect patients’ relevant family and personal histories, support their pre- and post-test counseling needs, and help return results. In addition, online tools that help clinicians interpret results, such as ASK2ME, allow clinicians without genetics expertise to use test results in clinical decision making. Multiple professional organizations are developing and implementing solutions to this challenge, including novel strategies for the delivery of pretest informed consent and genetic counseling.

As genetics and genomics are slowly becoming a part of mainstream care, these solutions could allow testing to be scaled to larger patient populations, with even more solutions on the horizon.

Another challenge to universal germline genetic testing is the likely accompanying increase in detection of variants of uncertain significance (VUSs), which may introduce ambiguity for clinicians managing care. Although initial clinician-reported studies found that 24%-50% of patients with breast cancer who had a VUS in BRCA1 or BRCA2 would receive the same management as patients with BRCA1 or BRCA2 PGVs, follow-up studies observed VUS results being handled not differently from negative results in patients with breast cancer in terms of changing physicians’ recommended treatment course. These data suggest that ongoing physician education can effectively mitigate this obstacle.

A criticism of providing MGPT for all patients with cancer is the wide variability in panel composition, which may lead to inclusion of moderate- and low-penetrance genes, potentially limiting the clinical implications of including such genes for testing. However, published management guidelines for several moderate- and even low-penetrance cancer risk genes do exist. Similarly, the INTERCEPT study identified PGVs in genes such as BARD1, RAD50, and BLM (monoallelic) that may not be known to increase cancer risks but, in already affected patients, confer potential eligibility for clinical trials of poly (ADP-ribose) polymerase inhibitors, suggesting that inclusion of these genes is warranted because of their potential treatment implications. Moreover, detection of PGVs in these genes initiates cascade testing (the key to prevention) for patients’ families.

Assessment of the clinical implications of MGPT suggests that clinicians should focus on the genes in the panels that they consider useful, on the basis of the published evidence. Preconstructed panels are not the only avenue to ordering multiple genes. Most, if not
all, commercial testing laboratories allow for customized panels to be ordered that are tailored to each patient. Although the data reviewed here are restricted to patients with solid tumors who underwent germline testing regardless of whether they met certain clinical criteria, there is also ample evidence of germline variants conferring cancer predisposition with potential implications for management in hematopoietic malignancies.88-90 A subset of these patients should certainly undergo germline testing, whereas more data on the value of testing all such patients accumulate.

In conclusion, burgeoning evidence has demonstrated that the current paradigm of limiting germline genetic testing to a subset of patients with cancer thought to be at the highest risk for HCS is not in the best interests of effective and data-driven patient care. Existing guidelines hamper access to testing for a substantial number of patients with cancer who should be receiving clinically actionable findings to help guide treatment of their current cancer, surveillance, and prevention of additional primary cancers in other organs. Knowledge of PGVs can support the use of targeted therapies, and the discovery of index cases in a family will prompt genetic counseling and cascade testing for at-risk family members. As the costs of next-generation sequencing continue to decrease, expanding MGPT for HCS to all patients with solid tumors not only is feasible but would also improve patient care and treatment.

AFFILIATIONS

1Invitae, San Francisco, CA
2Dana Farber Cancer Institute, Boston, MA
3Division of Clinical Cancer Genomics, Department of Medical Oncology & Therapeutic Research, City of Hope National Cancer Center, Duarte, CA
4Center for Individualized Medicine, Mayo Clinic, Phoenix, AZ
5Division of Gastroenterology and Hepatology, Department of Medicine, Mayo Clinic, Phoenix, AZ
6Department of Clinical Genomics, Mayo Clinic, Phoenix, AZ
7Carolina Urologic Research Center, Myrtle Beach, SC

CORRESPONDING AUTHOR

Robert L. Nussbaum, MD, Invitae, 1400 16th St, San Francisco, CA 94103; e-mail: robert.nussbaum@invitae.com.

EQUAL CONTRIBUTION

E.D.E., S.M.N., and S.L.B. contributed equally to this work.

AUTHOR CONTRIBUTIONS

Conception and design: Edward D. Esplin, Sarah M. Nielsen, Sara L. Bristow, Heather Hampel, N. Jewel Samadder, Neal D. Shore
Administrative support: Sara L. Bristow, N. Jewel Samadder, Neal D. Shore
Collection and assembly of data: Edward D. Esplin, Sarah M. Nielsen, Heather Hampel
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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Edward D. Esplin
Employment: Invitae
Stock and Other Ownership Interests: Invitae
Consulting or Advisory Role: Taproot Health Inc

Sarah M. Nielsen
Employment: Invitae
Stock and Other Ownership Interests: Invitae
Travel, Accommodations, Expense: Invitae

Sara L. Bristow
Employment: Invitae
Stock and Other Ownership Interests: Invitae

Huma Q. Rana
Research Funding: Ambry Genetics, Invitae

N. Jewel Samadder
Consulting or Advisory Role: Janssen Research & Development, Cancer Prevention Pharmaceuticals, Recursion Pharmaceuticals

Neal D. Shore
Consulting or Advisory Role: Bayer, Janssen Scientific Affairs, Dendreon, Tolmar, Ferring, Medivation/Astellas, Amgen, Pfizer, AstraZeneca, Myovant Sciences, Astellas Pharma, AbbVie, Merck, Bristol Myers Squibb/Sanoﬁ, Boston Scientiﬁc, Clovis Oncology, Exact Imaging, FerGene, Foundation Medicine, CG Oncology, Invitae, MDxHealth, Myriad Genetics, Nymox, Propella Therapeutics, Genzyme, Sanoﬁ, Sesen Bio, Exact Sciences, Genesis Cancer Care, Paciﬁc Edge Biotechnology, Phosphorus, UroGen Pharma, Specialty Networks, PeerView, Clarity Pharmaceuticals, Lanthus, Lilly, Photocure, Sema4, Telix Pharmaceuticals, Tempus, Vaxilion

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