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REVIEW ARTICLE

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Elective genomic testing: Practice resource of the National Society of Genetic Counselors

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Abstract

Genetic counseling for patients who are pursuing genetic testing in the absence of a medical indication, referred to as elective genomic testing (EGT), is becoming more common. This type of testing has the potential to detect genetic conditions before there is a significant health impact permitting earlier management and/or treatment. Pre- and post-test counseling for EGT is similar to indication-based genetic testing. Both require a complete family and medical history when ordering a test or interpreting a result. However, EGT counseling has some special considerations including greater uncertainties around penetrance and clinical utility and a lack of published guidelines. While certain considerations in the selection of a high-quality genetic testing laboratory are universal, there are some considerations that are unique to the selection of a laboratory performing EGT. This practice resource intends to provide guidance for genetic counselors and other healthcare providers caring for adults seeking pre- or post-test counseling for EGT. Genetic counselors and other genetics trained healthcare providers are the ideal medical professionals to supply accurate

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information to individuals seeking counseling about EGT enabling them to make informed decisions about testing and follow-up.

KEYWORDS
direct-to-consumer genetic testing (DTC), genetic counseling, genetic testing, population screening, predictive genetic testing

1 | INTRODUCTION

Genomic testing of individuals without a medical indication for testing, referred to here as elective genomic testing (EGT; Lu et al., 2019), represents a growing portion of the practice of genetic counseling. EGT may be ordered in a clinical setting by a healthcare provider, may be marketed directly to the consumer (DTC), or may be provided as a physician-mediated test. EGT is often consumer-initiated (CIGT; see Supplemental Document 1: Appendix S1). EGT is the logical extension of well-established screening practices, such as newborn screening (Dubay & Zach, 2021; Wilcken & Wiley, 2008), carrier screening (Chokoshvili et al, 2017; Gregg et al., 2021; Sparks, 2020), and secondary findings return (Bick et al., 2017; de Wert et al., 2021; Green et al., 2013; Kalia et al, 2016; Miller et al., 2021; Schwartz et al., 2018; Webber et al., 2018). The American College of Medical Genetics and Genomics (ACMG) has published points to consider statements regarding EGT in connection with both personal and population health (Bean et al., 2021; Murray et al., 2021). Genetic counseling for EGT employs many of the same principles as more traditional genetic disease testing (Schwartz et al., 2021). However, EGT presents unique counseling considerations, and there are no established guidelines for genetic counseling in this setting. This resource was created to provide a review of EGT counseling issues and to provide guidance for genetic counselors and other healthcare providers when encountering patients who have had or who plan to have EGT.

Individuals may pursue EGT to learn personally relevant health-related information, mitigate future health risks, satisfy general curiosity, and, where relevant, contribute to research (East et al., 2019; Linderman et al., 2016; Schmidt et al., 2019; Suckiel et al., 2016). Individuals pursuing EGT may self-refer, participate through a research study, or be offered testing through their health system (Anderson et al., 2021; Blout Zawatsky et al., 2021; Christensen, Bell, et al., 2021; Christensen, Schonman, et al., 2021; Cochran et al., 2021; David et al., 2021; Denny et al., 2019; Lemke et al., 2020; Machini et al., 2019; Sanford Imagenetics, 2020; Schwartz et al., 2018).

The difference between elective and diagnostic testing lies in test design, how the results are analyzed, and the indication for the test. Whereas diagnostic testing is designed to thoroughly evaluate the known genetic contributions related to a specific phenotype, EGT is usually analyzed independently of phenotype or family history. EGT can be designed to evaluate any medical (e.g., genes connected to a particular condition, such as hereditary colon cancer) or nonmedical aspects of human genetics (e.g. ancestry; Table 1; Bean et al., 2020). Because phenotype is not sought for most EGT, and because the a priori risk in an unselected population is significantly lower than that in individuals tested for a medical indication, only pathogenic and likely pathogenic variants are generally returned (Lu et al., 2019). EGT may have limited analysis and interpretation, automated interpretation, or may only provide raw data to consumers to explore on their own through various online third-party interpretation tools (Badalato et al., 2017; Lu et al., 2019; Nelson & Fullerton, 2018). It is important to understand the limitations of the technology used in testing, for example, an array compared with sequencing (Supplement 2: Appendix S1). Because EGT is a screening test, it is most appropriate for those who do not have a personal or family history of a medical condition that may benefit from indication-based testing. Genetic counselors can play an important role in helping individuals understand whether EGT or a diagnostic test is more appropriate (Anderson et al., 2021).

Studies suggest that when whole genome or exome sequencing is performed in an elective setting, approximately 11.5% of individuals will have a variant associated with their personal medical history, and 10%–15% will have a pathogenic or likely pathogenic variant for a monogenic disorder that has an impact on the individual's care, most often unsuspected before testing (Anderson et al., 2021; Ceyhan-Birsoy et al., 2019; Cochran et al., 2021; Haverfield et al., 2021; Hou et al., 2020; Machini et al., 2019; Maxwell et al., 2020). Over 85% of those tested will carry an autosomal recessive or X-linked disorder (Ceyhan-Birsoy et al., 2019; Cochran et al., 2021; Machini et al., 2019), and 95% or more will have variants associated with abnormal metabolism of certain drugs (Chanfreau-Coffinier et al., 2019; Cochran et al., 2021; Machini et al., 2019). Additionally, EGT can be used to calculate polygenic risk scores (PRS) for common medical conditions, such as heart disease and cancer (Kachuri et al., 2020; Kapoor et al., 2020; Khera et al., 2017; Neumann et al., 2021; Roselli et al., 2020) and to address nonmedical questions, such as ancestry (Kling et al., 2021).

2 | CONSIDERATIONS WHEN EVALUATING AN ELECTIVE TESTING LABORATORY AND TEST

Elective genomic testing should meet the same analytical performance as standard genetic testing if it is to be used for medical management. However, the challenge faced by laboratories offering EGT is the need to provide elective testing at a lower price point to enable access due to lack of insurance coverage. This can create the

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TABLE 1 Likelihood of detecting various EGT results and their medical relevance: this table outlines various types of EGT findings, if the finding is or is not expected to be medically relevant, and the likelihood a finding would be identified if WGS or WES is performed.

Type of finding	Medical relevance	Likelihood of finding[b]	Example	References
Actionable monogenic disease	Today	Low	Hereditary breast and ovarian cancer	Petrucelli et al. (1998)
Non-actionable monogenic disease	Today	Medium	Huntington's disease	Caron et al. (1998)
Risk allele[a]/Low penetrance variant	Today	Medium	Factor V leiden; hemochromatosis C282Y; biotinidase D44H; apolipoprotein e4	Barton and Edwards (2000), Kujovich (1999), Rao et al. (1996), Wolf (2000)
Carrier status	Today	High	Cystic fibrosis transmembrane conductance regulator (CFTR) Carrier	Machini et al. (2019)
Pharmacogenomics	Today	High	CY2C19 metabolizer status	Pratt et al. (2018), Scott et al. (2013), Van Driest et al. (2014)
Blood/platelet typing	Today	High	ABO/Rh status and platelet-leukocyte aggregation	Westhoff (2019)
HLA status	Today	High	Transplant matching/pharmacogenetics	Bravo-Egana et al. (2021), Phillips et al. (2018)
Actionable microbiome	Emerging	Low	*Clostridium difficile*	van Prehn et al. (2021)
Viral detection	Emerging	Low	Presence of CMV in newborns	Beswick et al. (2019), Goderis et al. (2014)
Protective allele[a]	Emerging	Low	Proprotein convertase subtilisin/Kexin type 9 serine protease (PCSK9) R46L	Benn et al. (2010)
Polygenic risk score	Emerging	High	Coronary artery disease risk score	Elliott et al. (2020), Khera et al. (2018)
Ancestry	Recreational	High	% North African	Wang, Lambert, et al. (2021), Wang, Song, et al. (2021)
Phenotypic trait	Recreational	High	Ear wax	Rodriguez et al. (2013), Yoshiura et al. (2006)
Nutrigenomics	Future	Unknown	Vitamin D metabolizer status	Carlberg (2019)

Note: Examples of each type of finding are provided as well as references.

[a]We used the terminology as recommended by the ClinGen Low Penetrance/Risk Allele Working Group (https://clinicalgenome.org/site/assets/files/4531/clingenrisk_terminology_recomendations-final-02_18_20.pdf).

[b]Based upon current technology and scientific knowledge: Low ≅ <10%; medium ≅ 10% < X < 90%; high ≅ >90%.

need for performance trade-offs in several areas. Regulatory frameworks do not mandate specific performance thresholds, and as such, it is critical that providers are aware of key performance metrics before selecting a laboratory. For example, it is not mandatory to confirm variants by other testing methodologies prior to reporting and if this is not part of the test, understanding the test's analytical false-positive rate is key. Regulators do mandate that laboratories disclose analytical performance as well as test limitations, but there is substantial variability in how well this information is summarized (Santani et al., 2018). No basic testing standards nor individual or data protections should be assumed until the laboratory, the genetic test, and the testing process have been evaluated.

Below and in Figure 1, we provide points to consider when critically evaluating the quality of a laboratory, its services, and the clinical and analytic validity of the tests offered to enable informed test selection or to determine appropriate post-test recommendations. Supplemental Document 3: Appendix S1 provides a list of detailed questions that providers can ask as laboratory websites or sample reports may not provide sufficient depth, necessitating talking to qualified laboratory staff such as the laboratory director.

2.1 | Laboratory quality and transparency

Reputable laboratory websites disclose information regarding test design, testing processes, variant detection rates, analytical/clinical performance, test cost and turnaround time, as well as test limitations, and have sample reports readily available. At a minimum, the laboratory should provide contact information for sending an inquiry to the lab, specifically to the laboratory director. Services that provide interpretation of raw data may not have laboratory directors on staff, at which point, the inquiry should be directed to other appropriate staff (e.g., bioinformatician).

Laboratories that carry out EGT for clinical purposes must be certified by the Centers for Medicare and Medicaid Services when ordered by a physician, and many of these laboratories are also CAP-accredited (CMS, 2021). Health-related EGT may be regulated by the Food and Drug Administration (Moneer et al., 2021). Laboratory licenses (e.g., CLIA), accreditations (e.g., CAP) and any state-specific approvals (e.g., NYS) should be readily available. It is increasingly common for laboratories to outsource parts of the testing process (e.g. sequencing may be carried out by an external entity). In those

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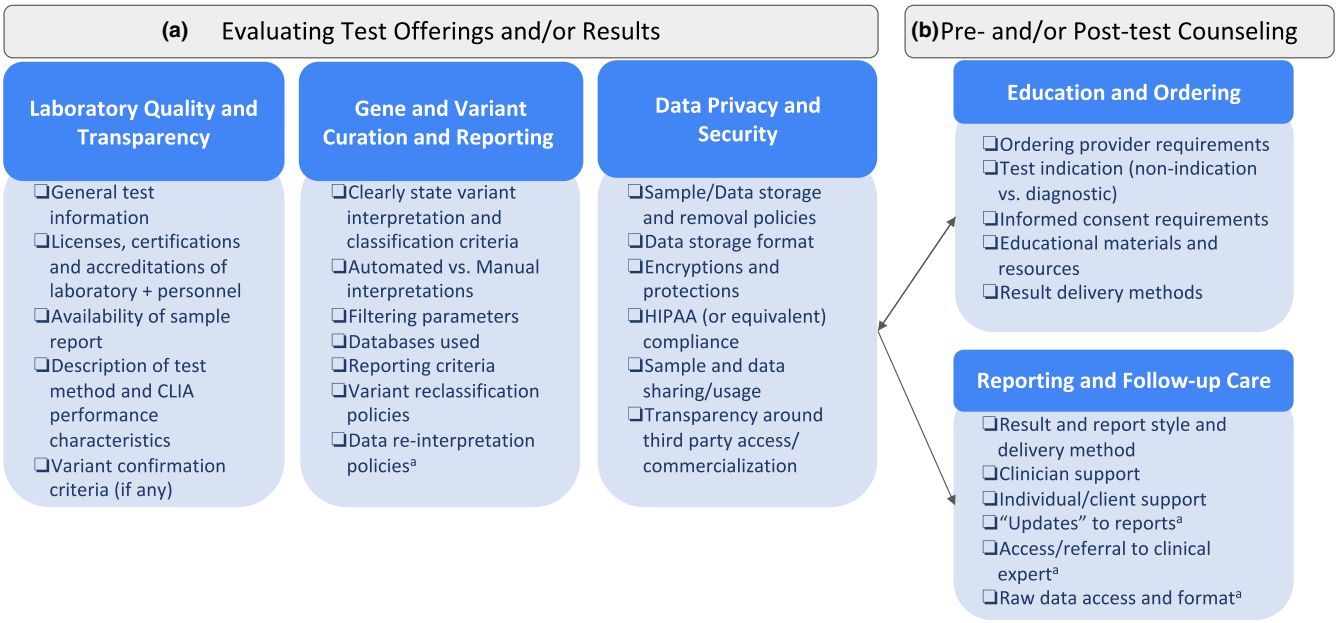

FIGURE 1 Considerations when evaluating a laboratory and testing: Panel a represents criteria that should be assessed when either evaluating a test offering OR when interpreting a result. These criteria may affect validity of a result, as well as follow-up care for an individual, including informing individuals of data usage policies that they may not be aware of. Panel b represents criteria that can vary and do not affect interpretation of a result but may be addressed during counseling and can impact follow-up decision-making. +, May incur additional fees. CLIA, Clinical Laboratory Improvement Amendments; EGT, Elective genomic testing; HIPAA, Health Information Portability and Accountability Act. For elaboration and detailed guidance when evaluating EGT laboratories and tests, see Supplemental Document 1: Appendix S1.

instances, licensures of all entities need to be available to verify that the test result is fully clinical grade to formulate next steps. For further discussion of the evaluation of laboratories and EGTs, please see Supplemental Document 2: Appendix S1.

2.2 | Methodologies for EGT testing and testing limitations

Just as with traditional genetic testing, there are various methodologies that can be used for EGT. Current methods of testing for EGT most commonly include (1) genotyping via array, which looks at specific variants, often spread throughout the whole genome, and (2) sequencing, which looks at most variation across either specific genes of interest, the entire exome, or the entire genome. For exome and genome data, results are still typically limited to a smaller set of gene regions with known disease association. Different methodologies have different levels of performance for sensitivity depending upon the type of variation. Please see Supplemental Document 2: Appendix S1 for more details.

3 | RESULT INTERPRETATION AND REPORTING PRACTICES

Variant interpretation and reporting thresholds for the test should be transparent. Reporting thresholds are typically composed of both quality thresholds (e.g., a minimum number of reads containing a variant) and interpretation thresholds (confidence levels of interpretation). Variants should be classified using current best practices recommended by bodies, such as ACMG, AMP, or ClinGen, which are updated regularly (Rehm et al., 2013; Richards et al., 2015). EGTs may use automated or manual interpretation, which can influence a health professional's interpretation of a result. Automated interpretation implies that a variant classification is compiled based on various databases or annotation sources, such as ClinVar (Landrum et al., 2016, 2018), while manual interpretation refers to a variant classification that has been reviewed by an ABMG-board-certified professional. While many tests employ automated tools throughout the testing process, final review of a result by a board-certified geneticist provides further credibility (Adams et al., 2016).

Interpretation thresholds for EGTs are often limited to pathogenic and likely pathogenic findings (P/LP). In indication-based testing, these two classification categories are usually deemed equivalent (Harrison & Rehm, 2019). This is not the case in patients without a medical indication or a family history of disease. Here, even a slight reduction in the interpretive accuracy of a variant (e.g., a variant is inaccurately classified as LP) can have very significant implications for the positive predictive value thereby impacting the true risk to the patient (Biesecker, 2019; Hagenkord et al., 2020). In the screening test setting, a reduction in a priori risk leads to increased occurrence of interpretive false-positives (Hagenkord et al., 2020). Therefore, LP variants in the EGT setting may warrant higher scrutiny prior to taking clinical action.

Some tests may report variants of uncertain significance (VUS) in certain scenarios; therefore, it is important to understand in the pre- or post-test setting when a VUS may or may not be reported

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(Petrucelli et al., 2002). In the setting of secondary genomic findings, it has been recommended not to report VUS nor use them for medical management (Miller et al., 2021; Richards et al., 2015). We also recommend that VUS not be reported in the setting of EGT, unless a phenotype is present and provided to the laboratory, although specific laboratory practices will vary. A common source of VUS are genes whose disease associations have not been firmly established (genes of uncertain significance, GUS). Recent guidance by the ACMG cautions against the inclusion of GUS, even in diagnostic sequencing panels (Bean et al., 2020). Although formal guidance for EGT has not yet been established, providers should review a laboratory's gene inclusion criteria and variant classification reporting thresholds prior to ordering a test. When interpreting VUS or GUS, if it is determined that the individual has a related clinical phenotype, then further evaluation with clinical diagnostic testing may be warranted (Petrucelli et al., 2002). Additionally, given the known discordance rates of variant classification, the provider may perform their own variant interpretation or seek a second opinion (Amendola et al., 2021). Risk alleles, carrier status, pharmacogenomic profiling, and recreational findings may also be reported and may have different interpretation or quality thresholds.

Policies for variant reclassification should be readily available upon request. These policies may range from not including any reclassification updates, to periodic variant review and notification to updating only upon reclassification of another sample detected by the lab.

4 | PRE- AND POST-TEST EDUCATION AND COUNSELING

Any individual wishing to have an EGT consultation should be offered a referral to a genetics provider familiar with EGT, or to another healthcare professional who is trained to educate and consent individuals and facilitate informed decision-making related to EGT

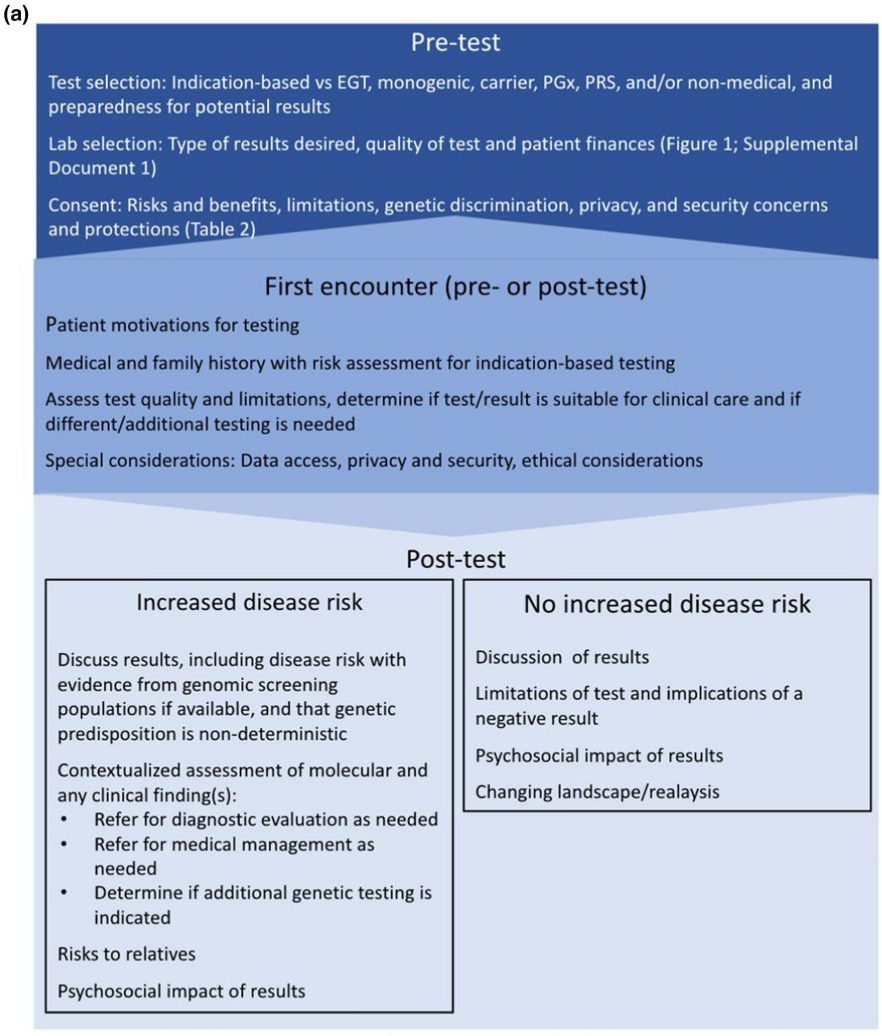

FIGURE 2 Genetic counseling considerations for elective genomic testing: Panel a represents important high-level considerations when providing pre-test genetic counseling (dark blue), and post-test counseling (light blue), as well as considerations at both time points (medium blue). Panel b represents the flow of a patient who either presents seeking EGT or with EGT results seeking counseling. EGT, Elective genomic testing; PGx, pharmacogenomics; PRS, polygenic risk scores

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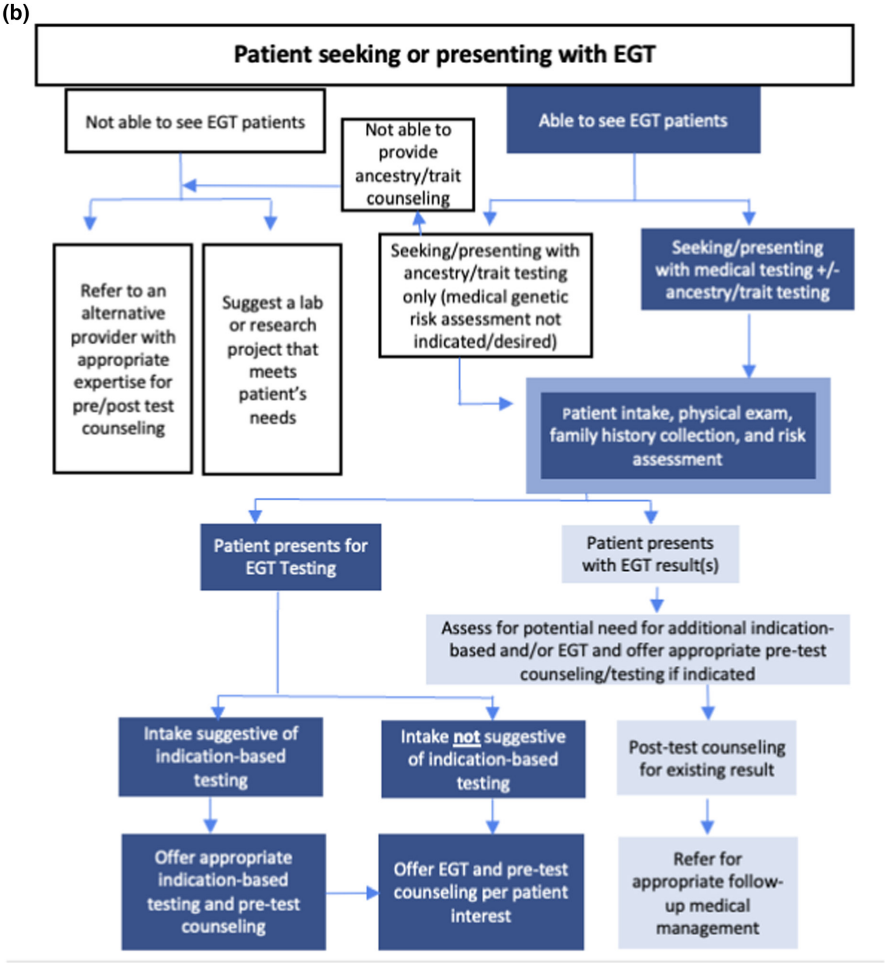

FIGURE 2 (Continued)

(Figure 2). Accurate interpretation of test results and follow-up recommendations are best performed by these providers. In addition to the improved patient experience counseling provides, there is also a risk of misinterpretation of genetic test results by non-genetics providers, leading to inappropriate medical care and misdiagnosis (Ayala-Lopez & Nichols, 2020; Tandy-Connor et al., 2018). Genetic counselors are well-positioned to minimize this potential risk. Guidance has been published to help providers decide when a full genetic counseling session might be most useful for consent and disclosure (Ormond et al., 2019). It is essential that individuals receive all of the information needed to make an informed decision to consent to EGT prior to testing regardless of the platform used for pre-test counseling and/or education.

GCs may be in the position of discussing EGT results with patients within their own clinical practice, or as an employee of a lab or contracted service, an increasing number of which offer genetic counseling services, especially in the post-test setting. Regardless of the setting, genetic counseling for all EGT largely follows the same structure as a typical genetic counseling session (Hampel et al., 2015).

Due to the growing demand for access to genetic counselor expertise (Hoskovec et al., 2018; Jenkins et al., 2021), as EGT scales, it will likely require the assistance of other healthcare providers, such as primary care providers. Genetic counselors can assist in these cases by building relationships with non-geneticist healthcare providers interested in offering EGT. Genetic counselors are also well positioned to create educational resources, such as online resources to assist in educating providers and the public about EGT. By serving as both an educational and consultative resource, genetic counselors can leverage and promote their knowledge to expand the impact of high-quality EGT and genomic screening.

4.1 | Pre-test

Pre-test counseling and/or education is an important cornerstone of informed consent, including for EGT. Studies have shown that individuals benefit from having genetic counseling prior to EGT (Suckiel et al., 2016). Providers seeing patients for pre-test counseling should review the risks and benefits of EGT (Table 2) and other important considerations addressed in this manuscript. When pre-test counseling is performed, a detailed medical and family history should be collected to assess if an individual meets criteria for indication-based testing, and the proper test should be selected based on indication and the individual's elective testing goals (Figure 2).

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TABLE 2 Benefits and risks of elective genomic testing. This table outlines benefits and risks of elective genetic testing.

Benefits	Details
May identify health-relevant genomic test results	• Identifies patients who *might not have otherwise known they were at risk*, such as those who do not meet criteria due to family size, lack of personal or family health history knowledge, adoption, etc. (Abul-Husn et al., 2016; Beitsch et al., 2019; Buchanan et al., 2020; Grzymski et al., 2020; Neben et al., 2019) • *May improve morbidity and mortality if* health-relevant genetic variants are identified, especially those with clear medical actionability (Domchek et al., 2010) • The EGT process may uncover personal or family history that warrants *additional indication-based testing*
Societal engagement in genetics	• May increase engagement with and knowledge of genetics (van den Akker et al., 2019) • Increased familiarity with genetics by healthcare providers may increase appropriate genetics referrals.
Patient autonomy	• Driven by patient preference and thus may give patients a greater sense of control over health (Horton et al., 2019) • May give patients ownership or increased control over the use of their genomic data (Kirkpatrick & Rashkin, 2017) • Patients may feel EGT results are useful to inform lifestyle changes (Roberts et al., 2018) • EGT may provide an option for those wishing to keep genetic test results out of their medical record due to concerns about privacy and genetic discrimination (Green et al., 2015) ○ Extensive pre-test education should be offered to such patients, given the existing protections and potential risks in delays to appropriate post-result care as addressed in the Risks section.
Patient access	• Traditional clinical genetic testing is not always accessible to individuals with a medical indication for testing due to barriers like cost, wait times or location; EGT increased cascade testing uptake in one study (Caswell-Jin et al., 2019) ○ Caution and extensive lab communication should be taken in these scenarios, given possible limitations in testing methodologies as addressed in the Risks section.
Risks	**Details**
Comprehensiveness and/or quality may be lower or more difficult to assess	• Assays directed at healthy consumers may be less comprehensive for the conditions or genes of interest (Lu et al., 2019) • Results may be less accurate from tests performed by laboratories that do not comply with regulations such as CLIA and CAP, and/or do not publish clinical utility and validity data
May occur outside of genetic counseling or healthcare context	• Genetic counselors and other genetics trained healthcare providers are uniquely qualified to provide psychosocial and educational support for patients interested in EGT (Wolff & Wolff, 2018) • Ideal patient experience may include comprehensive, pre-test counseling (NSGC, 2019) • Greater risk for result misinterpretation outside of a healthcare setting (Farmer et al., 2019) • At-home genetic testing may increase risk of fraudulent sample identity • Recommended specialist follow-up may be more difficult to facilitate if results are obtained outside of a clinical setting
May lead to inappropriate medical care	• Unclear medical implications in genes with no appreciable phenotype, variable penetrance, and/or no published evidence-based guidelines • Uncertainty about the penetrance of some pathogenic variants identified in unselected, healthy populations (Bean et al., 2021; Forrest et al., 2021; Hagenkord et al., 2020; Lu et al., 2019; Murray et al., 2020; Natarajan et al., 2016) • Patients or non-genetics providers may misinterpret results, and over- or under-react to the findings. • Results may be inaccurate or incomplete for conditions of interest • Raw data from EGT often easily available, and if analyzed by a third-party database, may lead to misinterpretation, anxiety, and unnecessary or inappropriate medical interventions
Access is not fully equitable or private	• May be cost-prohibitive, as EGT is largely not covered by insurance at this time. Follow-up medical care also may not be covered (Aetna, 1998; Cross, 2021; Matloff, 2018). • Some EGT requires access to computer or other device, email, and stable internet connection • Relevant EGT results must be shared with healthcare providers and payers to facilitate appropriate interventions based on result • Some EGT companies sell consumer data, for example to pharmaceutical companies. Additionally, some companies reveal identifiable data to other users and/or law enforcement (Hendricks-Sturrup et al., 2019)

Abbreviations: CAP, College of American Pathologists; CLIA, Clinical Laboratory Improvement Amendments; DTC, Direct to Consumer; EGT, Elective Genomic Testing; HIPAA, Health Information Portability and Accountability Act.

Some existing providers and clinics see patients for pre-test counseling for EGT (Brigham and Women's Hospital, 2020; Cochran et al., 2021; Mayo Clinic, 2016; UCSF Health, 2021), and one small study reports this type of encounter, which includes collection of a thorough medical and family history and physical exam, takes an average of 71 minutes (Cochran et al., 2021). As EGT is scaled to the population level, traditional pre-test genetic counseling delivered via in-person or telemedicine will present feasibility issues due to the

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time and financial resources required. Many EGT companies have attempted to tackle this issue by offering pre-test education via videos, educational website pages, chatbots, blog posts, and email campaigns. Though these resources may offer valuable education, they do not always meet genetic counseling standard of care best practices (Greenberg et al., 2021). Important components of pre-test education for EGT offerings include, if applicable (Figure 2a): accuracy and limitations of the test, review of the types of possible results and the likelihood to receive each result type; discussion around the types of variants that will be returned and the implications of these variant types (i.e., is the lab returning only P/LP variants or are they returning VUS, and if they are returning the latter, what are the implications); potential implications for family members; review of the Genetic Information Non-Discrimination Act (GINA) and state-specific nondiscrimination laws and their protections/limitations (Green et al., 2015), and other privacy and security considerations based on the laboratory's policies and processes (Arshad et al., 2021; National Comprehensive Cancer Network, 2020).

4.2 | Post-test

Post-test counseling should be available to individuals who have had EGT (Figure 2). An individual may present for post-test counseling after already having pre-test counseling or may preseont having pursued EGT without the involvement of a healthcare professional. While genetic counselors may not always feel comfortable discussing such results with patients (Hsieh et al., 2021), post-test counseling for EGT shares many of the same core counseling principles as counseling for traditional genetic testing.

Prior to interpreting EGT results for a patient, it is important to assess the quality, comprehensiveness, and limitations of the test conducted (see "Considerations for evaluating an elective testing laboratory and test" section above), particularly when using results for medical decision-making. It may be necessary to request test results prior to post-test counseling for case preparation. For some patients, additional genetic testing may be indicated to validate findings or because of residual medical risks. For complex cases, it may be necessary to have multiple genetic counseling sessions or refer to another specialist with expertise in the area of need. In addition, if an individual presents with questions about their raw data, providers should be prepared to discuss the limitations of raw data interpretation databases (see Section 6, below). For patients for whom post-test counseling is the first encounter or for those with limited pre-test counseling, contracting and the collection of personal and family history information is important to understand why the patient engaged in EGT, what they hope to achieve with genetic counseling, and relevant information for contextualizing results with the patient's history.

Outside of a traditional clinic setting, post-test education can be delivered via multiple mechanisms for patients undergoing EGT. For example, many companies offering such tests develop their test result reports for the patient audience, rather than clinicians (Lachance et al., 2010). Individuals may access EGT results via an online patient portal. Beyond the report, clinical services add significant value to the patient experience in terms of result understanding as well as medical and psychosocial support. Some laboratories offering EGT employ genetic counselors for report review or refer patients to third-party genetic counselors. All labs offering EGT should strongly consider making genetic counseling by certified genetic counselors available, for all individuals but particularly for patients with medically actionable findings.

In the clinical setting, the approach to post-test genetic counseling for patients with EGT depends upon the context with which the patient has presented for care, including whether post-test counseling is the first genetics encounter for that patient. Patients who receive EGT through an interaction with a qualified provider may have had an opportunity to engage in important components of genetic counseling prior to result receipt (Figure 2). If so, post-test counseling can focus on a discussion of the results received and the corresponding personal and medical implications for the patient. In one small study, post-test counseling took an average of 56 min in this context (Cochran et al., 2021).

Some individuals may present for post-test counseling for nonmedical EGT findings such as trait information, ancestry, or unanticipated familial relationships. Pre- and post-test education and support can be just as important in such instances as for health-related tests. Ancestry results can have significant and sometimes devastating implications, including the discovery of new family members or unexpected relationships (Crawshaw, 2018; Larmuseau, 2019), and can be an emotional experience because of the historical mistreatment of certain ancestral and ethnic groups (Copeland, 2021). Trait information can also provide insights that may impact patients' self-reported health behaviors, especially as it relates to diet (Nielsen et al., 2017). Regarding nutrigenomics and other traits that might impact patient health and behavior, it is just as important to understand the underlying science behind the result when helping an individual to understand their report and interpret the implications correctly. Information from trait and ancestry testing that does not match the patient's lived experience can also lead to mistrust in genetic testing in general, which could impact their trust in accurate health-related test results. Genetic counselors are uniquely qualified to offer result interpretation, as well as psychosocial and medical support to patients with these types of EGT results. Involvement of a physician with expertise in genetics may provide further guidance around variant interpretation, as well as evaluation of the patient and provision of recommendations for medical follow-up when a pathogenic or likely pathogenic variant is detected. Millions of individuals have already undergone such testing (Regalado, 2019), and it is reasonable to predict that the number of patients seeking such expertise will increase in the future as demand grows (Amendola et al., 2021; Ruhl et al., 2019). Just as in other specialty areas, some genetics providers have developed expertise in counseling for various nonmedical applications of EGT and are available for referrals (Kirkpatrick & Rashkin, 2017). Continuing education material may also be available for those interested in gaining expertise in these and other emerging areas.

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5 | COST AND INSURANCE COVERAGE

While the cost of molecular testing has dramatically decreased since the completion of the Human Genome Project, EGT is not typically covered by private or public insurance in the U.S. at the time of this publication, due to limited evidence regarding clinical utility (Vassy, Christensen, Slashinski et al., 2015). This may change with larger scale studies examining clinical utility and the costs and benefits of EGT, and indeed, some studies have attempted to evaluate cost-effectiveness of different approaches to genomic screening (Christensen, Phillips, et al., 2018; Christensen, Vassy, et al., 2018; Lacaze et al., 2019; Mackay et al., 2020; Vassy et al., 2017). Additionally, for some individuals seeking EGT, closer evaluation of the personal or family history will reveal an indication for diagnostic genetic testing which may be eligible for insurance coverage. Some individuals presenting with test results from a non-CAP/CLIA laboratory or interpretation pipeline may wish to undergo clinical confirmation of their results. They should be made aware that as of the writing of this paper, no standards exist for determining medical necessity in this situation and though some insurances may cover this (Aetna, 1998; Cross, 2021), they may be therefore responsible for the cost of confirmatory genetic testing.

Notwithstanding known general barriers to reimbursement for genetic counseling (Gustafson et al., 2011; Spinosi et al., 2021), a genetics consultation and risk assessment performed pre- or post-testing should be within the scope of coverage for most payors, even in the setting of EGT. Pre-test counseling may reveal an indication for diagnostic genetic testing. Post-test genetic counseling coverage is especially important for a P/LP medically actionable variant, detected by EGT, evaluated by a clinical laboratory that meets CAP/CLIA standards. As with any clinically confirmed medically actionable variant, subsequent risk management based on evidence-based recommendations and/or professional guidelines may be considered medically necessary, and out-of-pocket cost would depend on an individual's own insurance coverage and specific plan. Post-test genetic counseling may also be valuable if no variant is identified to contextualize the negative result to the individual's personal and family history and provide proper residual risk counseling.

6 | RAW DATA ACCESS AND USE

The discussion about data access naturally raises concerns surrounding data privacy and security. Genomics laboratories that are CLIA-certified and CAP accredited must follow established HIPAA privacy policies and procedures that protect health information (Evans & Wolf, 2019). Non-CLIA labs are not subject to these same regulations.

Additionally, patient and provider access to raw genetic data from EGT varies by the company or lab offering the testing. The genomic data that are shared may come from different steps of the process and may be available in different data formats. Please see Supplemental Document 3: Appendix S1 for details on specific file types. Raw data files are commonly made available by EGT companies with array-based platforms, though sequencing-based files are increasingly becoming available as well. These raw data files may then be further annotated using third-party interpretation tools (Allen et al., 2018; Wang et al., 2018). However, the raw data may contain false-positive variants that were not evaluated by the laboratory. This is a concern, as misannotations stemming from inaccurate raw data can lead to false-positive results for medically relevant variants (Tandy-Connor et al., 2018). Further, as these annotation tools are typically web portals where users upload their data to be automatically annotated (often for a fee), they may include information that has not been well-curated and/or that draws from summaries of scientific studies which are not readily interpretable by the end user. Some companies offer wellness advice, consulting, or supplements specific to output from these tools. It is important that individuals using these databases understand potential limitations of the data and resulting recommendations. Additionally, the tools frequently do not describe how they may use or sell user data in their terms of service. We urge caution when individuals are uploading their raw data into third-party services and support the NSGC position statement on Raw Data (National Society of Genetic Counselors, 2020).

7 | EQUITY

While concerns about equity and exacerbation of healthcare disparities are pertinent to all types of genetic testing (Jooma et al., 2019), they may be particularly salient when considering tests that are generally only available by self-pay. Consumers must not only be able to afford the test but should also have access to referrals for genetic counseling and appropriate follow-up care. Individuals have the potential to face the same types of access barriers and racial/ethnic disparities as have been described for indication-based referrals and genetic testing (Carroll et al., 2020; Manrriquez et al., 2018; Williams et al., 2019).

One of the main concerns surrounding EGT, and indeed genetic testing in general, relates to a dearth of data from individuals of non-European descent (Popejoy & Fullerton, 2016). Efforts are underway to better characterize genomic variation in diverse populations (Wojcik et al., 2019), however, the current gap in understanding may lead to more ambiguity in the interpretation of genomic test results in non-European ancestry groups. These limitations may lead some individuals to perceive their risk to be higher or lower than is realistic and should be addressed in the report and pre- and/or post-test genetic counseling.

Array-based tests may be particularly susceptible to these limitations if they primarily include SNPs identified in well-described populations primarily of European ancestry. For example, PRS for common diseases have come under scrutiny for lower accuracy in individuals with non-European ancestry (Martin et al., 2019). Additionally, genes that disproportionately affect non-European ancestry groups due to founder variants may have been overlooked for inclusion on EGT panels. EGTs may focus on genes associated

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with conditions known to be prevalent in European ancestry populations, such as *BRCA1* and *BRCA2* (hereditary breast and ovarian cancer), and *HFE* (hereditary hemochromatosis) rather than in others, such as *TTR* (hereditary transthyretin amyloidosis; Abul-Husn et al., 2021; Damrauer et al., 2019; Miller et al., 2021; Centers for Disease Control, 2014). Some EGT companies and biobanks returning results are beginning to shift this paradigm (23andMe, 2019; Abul-Husn et al., 2021), and diverse stakeholders will need to continue to be engaged to ensure that consumers from ancestrally diverse backgrounds receive the same value from EGT as their European ancestry counterparts. The National Institutes of Health has recognized this issue and is funding research projects focused on the recruitment of diverse individuals (Amendola et al., 2018; Ganguly, 2020; Mapes et al., 2020). It is important to address these limitations and concerns with patients presenting for post-test genetic counseling, who may have accessed this type of testing without the benefit of robust pre-test education and counseling.

8 | OTHER ETHICAL CONSIDERATIONS

There are a number of ethical considerations related to EGT, some of which are specific to this type of testing and others that are broader issues in the field of genetics and genomics.

Critics of EGT highlight that there is not yet proven clinical utility for this type of testing and that EGT may lead to unnecessary clinical screening and costs to the medical system (Vassy et al., 2017). However, the understanding of clinical utility may vary between different stakeholders, such as providers, patients, and insurance companies, and experts are working to standardize the evaluation of clinical utility in the context of genomic testing (Hayeems et al., 2021). Additionally, early data suggest that EGT may not lead to significant short term follow-up care cost increases (Christensen, Phillips, et al., 2018; Christensen, Vassy, et al., 2018; Hart et al., 2018; Zhang et al., 2019), but larger longitudinal studies are needed before this question can be answered.

The location of a patient is also important to consider as international differences in opinion exist on the value of the return of results from the opportunistic screening of clinical or research genetic data, a context with some similarities to EGT. Such differences may influence the impact of EGT on the patient care experience and the healthcare system. Some groups such as the European Society of Human Genetics and the Canadian College of Medical Genetics do not support the return of secondary findings (Boycott et al., 2015; de Wert et al., 2021), while others like the ACMG, Genomics England, the French Society of Predictive and Personalized Medicine and the Global Alliance for Genomics and Health have supported the return of medically actionable results in certain contexts (Knoppers, 2014; Lewis et al., 2021).

Because EGT can occur independently of a healthcare provider, the results may not reach the medical record. If the individual then seeks appropriate medical management and treatment based on medically actionable EGT results, management and treatment may be delayed by the lack of integration with the healthcare system (Table 2).

Individuals pursuing EGT may not be aware of or fully understand the extent to which a genetic testing company retains rights to genomic data once sequencing has been performed. The "fine print" in consent forms for genetic testing may allow the testing company to share or profit from individuals' genomic data, which does not have any direct benefit to the individual being tested (Roland, 2019). Patients should always be strongly encouraged to fully read consent forms and ask any remaining questions to the company or their pre-test counseling provider. Patients choosing EGT or submitting their data to a third-party service should be counseled on whether and how the laboratory/service may sell or share user data on the individual level or in aggregate. In addition to commercial uses, recent high profile EGT testing cases have also highlighted the potential for law enforcement to obtain and use genetic data from commercial testing laboratories and other genomic databases, such as those used for genealogy, which has the potential to impact identification of other biological relatives without their knowledge (Guerrini et al., 2018; Kennett, 2019; Skeva et al., 2020).

Genetic testing in children is known to be a sensitive issue, as it balances the potential benefits to the child and their family against a child's right to make their own decisions in adulthood (AAP Committee on Bioethics, AAP Committee on Genetics, & American College of Medical Genetics Social Ethical and Legal Issues Committee, 2013; American Society of Human Genetics Board of Directors & American College of Medical Genetics Board of Directors, 1995; Botkin et al., 2015; Holm et al., 2019; Ross & Clayton, 2019). Many clinical EGT laboratories will not perform this type of testing for minors. As with any genetic testing, it is important when considering EGT in minors that their parents fully understand the risks and benefits, and that age-appropriate assent is obtained from the child.

9 | WHAT ADDITIONAL RESEARCH IS NEEDED TO ADVANCE THE FIELD?

9.1 | The changing technical landscape

EGT is rapidly evolving. The cost of sequencing is falling, making EGT more affordable. As a result, the counseling community can expect the number of individuals choosing EGT to grow. Long-read sequencing will soon become the prevailing methodology because it can accurately assess regions of the genome that short-read technology cannot (Mantere et al., 2019). This will expand the range of variants returned through EGT from single-nucleotide variants, indels, and copy number variants (Marshall et al., 2020) to include structural variants, trinucleotide repeats, variants affecting methylation, regulatory variants, and microRNA. These variants may be health-related or not and have a broad range of health implications and likelihood of being identified (Table 1). Further research on several key questions will inform the timescale and laboratory policies regarding EGT and will ultimately help to inform standard of care practice including:

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- When should an individual be re-sequenced? Should this occur as NGS accuracy improves to reach certain thresholds?
- Clonal hematopoiesis of intermediate potential (CHIP) is a potentially treatable hematopoietic stem cell disorder due to the age-dependent accumulation of somatic mutations that result in an increased risk of myeloid malignancies, cardiovascular disease and mortality (Asada & Kitamura, 2021; Heuser et al., 2016). The risk of CHIP is less than 1% before age 40 rising yearly to between 10% and 20% after age 70 (Jaisawal & Ebert, 2019). Individuals with CHIP are readily detected by genome sequencing from a blood sample. Should age be a factor in the decision to re-sequence?
- As knowledge of genomic variants improves and new phenotypes appear in the individual with age, should periodic re-analysis of existing sequencing data take place? How often?
- How and how quickly should EGT results be integrated into the electronic medical record to improve both routine and emergency care?

9.2 | Clinical utility of EGT results

The disease penetrance of some variants may be the same in unselected (i.e., healthy) individuals as it is for individuals with an indication for testing. However, for most variants, penetrance in unselected individuals is uncertain or may be low (Bean et al., 2021; Hagenkord et al., 2020; Lu et al., 2019; Murray et al., 2020). Recommendations for medical management and cascade testing of EGT recipients with an actionable variant may be distinct from the approach in existing guidelines that focus on individuals who receive results in the context of a personal or family history of disease, particularly if an individual's initial evaluation shows no evidence of disease (Murray et al., 2020). Provision of an accurate risk assessment and optimal health behavior recommendations to these individuals will require more data about the clinical utility of EGT results including:

- The short- and long-term health outcomes of individuals and their family members to calculate positive predictive value of these variants
- The cost-effectiveness of identifying these variants and implementing various management approaches (Christensen, Phillips, et al., 2018; Christensen, Vassy, et al., 2018; Zhang et al., 2019)
- The health behaviors of these individuals and their families (Christensen, Bell, et al., 2021; Christensen, Schonman, et al., 2021)

9.3 | Strategies for communicating results and limitations of EGT

Much has been learned about how to optimally communicate risk information (Fagerlin et al., 2011), and most patients adhere to health behavior recommendations after receiving negative genetic test results as long as the limitations are clearly communicated (Glanz et al., 2013; Grant et al., 2012; Petticrew et al., 2000). However, EGT may be distinct because it is often conducted without genetic counseling and the results may be less comprehensive and more uncertain than individuals pursuing testing believe they are. Further research is needed to better understand:

- The impact of EGT results (positive and negative) on an individual's understanding of health risks and recommended health behaviors
- The optimal role for genetic counselors in EGT (Bean et al., 2021), such as whether alternative modes of pre- and post-test counseling are non-inferior to genetic counseling
- How to engage individuals who have EGT results and are not aware of genetic counseling services
- How to educate more providers about genetics, as there are too few medical genetics professionals (Hoskovec et al., 2018; Jenkins et al., 2021)

9.4 | Leveraging EGT to promote accessibility

For precision medicine to apply to all, underserved groups need better access to genetics services. EGT provides an opportunity to study utilization of genetic testing in a different context. There is evidence that EGT rates for reasons such as ancestry (Carroll et al., 2020) are similar across non-Hispanic White, Hispanic, and non-Hispanic Black populations. Comparisons between individuals seeking EGT and traditional genetics services may provide insights about how to reach a wider range of individuals.

10 | CONCLUSION

EGT has many similarities to other forms of genetic testing, and genetic counselors have the skills and training to provide both pre- and post-test counseling for EGT in both clinical and nonclinical settings. There are many important considerations when evaluating a test and laboratory in both the pre- and post-test period. This field is rapidly evolving, and it is important for providers to remain diligent and stay up to date with the changing landscape when counseling patients about EGT, or to refer to providers specializing in EGT. Genetic counselors and other genetics trained healthcare providers are the ideal medical professionals to supply accurate information to individuals seeking counseling about EGT while supporting them to make informed decisions about testing and follow-up.

11 | PURPOSE

The goal of this practice resource is to provide genetic counselors (GCs) and other healthcare providers with guidance when providing services to adult individuals and families who are seeking pre- or post-test counseling for elective genomic testing. There are many nuanced issues that surround genomic testing in children and

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newborns that are not comprehensively covered by this resource. This resource is focused on health-relevant elective genomic testing, although it briefly provides an overview of recreational genomic testing. In this resource, the term "genomic testing" represents various types of genetic testing including genotyping and next generation sequencing (gene panels and exome/genome sequencing).

AUTHOR CONTRIBUTIONS

Carrie L. Blout Zawatsky: Conceptualization; methodology; writing – original draft; writing – review and editing. **David Bick:** Conceptualization; writing – original draft; writing – review and editing. **Louise Bier:** Conceptualization; writing – original draft; writing – review and editing. **Birgit Funke:** Conceptualization; writing – original draft; writing – review and editing. **Matthew Lebo:** Conceptualization; writing – original draft; writing – review and editing. **Katie L. Lewis:** Conceptualization; writing – original draft; writing – review and editing. **Ekaterina Orlova:** Conceptualization; writing – original draft; writing – review and editing. **Emily Qian:** Conceptualization; writing – original draft; writing – review and editing. **Lauren Ryan:** Conceptualization; writing – original draft; writing – review and editing. **Marci L. B. Schwartz:** Conceptualization; writing – original draft; writing – review and editing. **Emily R. Soper:** Conceptualization; writing – original draft; writing – review and editing. We would like to dedicate this manuscript to the memory of our co-author and esteemed colleague Lauren Ryan, without her this publication would not have been possible. The field of genetic counseling will miss her greatly.

CONFLICT OF INTEREST

NSGC requires systematic evidence review, practice guideline, and practice resource authors to complete a conflict of interest (COI) disclosure survey annually, starting at the formation of the author group. Authors must also report interim COI changes to the NSGC Practice Guideline Committee (PGC) within 30 days.

The PGC categorizes COI into two tiers. Tier 1 COI includes any direct, personal financial benefit that is ongoing or within the previous 12 months from a commercial entity that may benefit from the document. Tier 1 COI includes research funding from a commercial entity for 25% or greater of an author's salary. Tier 2 COI includes limited consultant roles, paid stipends/travel, and ongoing consultancy roles with companies that are involved in healthcare, but may not directly benefit from the document.

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Carrie Blout Zawatsky, Louise Bier, Katie Lewis, Marci Schwartz, and Emily Soper declare that they had no conflict of interest during the development of this practice resource. Lauren Ryan is a full-time employee of GRAIL, LLC, had a Tier 1 COI as a previous full-time employee of Color Genomics at the beginning of development (employment ended March 2021), and owns stock in GRAIL, LCC and Color Health, Inc. Ekaterina Orlova had a Tier 2 COI for contract work with Ariel Precision Medicine at the beginning of development, but no COI by Nov 2021. Emily Qian had a Tier 1 COI as a previous full-time employee of Veritas Genetics at the beginning of development (employment ended December 2019), but no COI by December 2020. David Bick has Tier 2 COI for consultancy work with HudsonAlpha Clinical Services Lab LLC, iRepertoire Molecular Lab, and Northwestern Mutual Life Insurance Company and was employed by Smith Family Clinic for Genomic Medicine until October 2021. Matthew Lebo has Tier 1 COI as a full-time employee of a not-for-profit molecular genetic testing laboratory (Laboratory for Molecular Medicine within Mass General Brigham). Birgit Funke had a Tier 1 COI for the majority of the development as a full-time employee for Veritas Genetics until December 2019 and Sema4 from March 2020 until present. KLL received salary support from the Intramural Research Program of the National Human Genome Research Institute, National Institutes of Health (NIH grant HG200387-08).

DISCLAIMER

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SUPPORTING INFORMATION

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

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Supplemental Document 1: Glossary of commonly used terms

Clinical Laboratory Improvement Amendments (CLIA) and Other Regulations: The Clinical Laboratory Improvement Amendments (CLIA) of 1988 requires laboratories to be certified to offer patient testing (CDC, 2018). CLIA laboratories conducting complex testing must seek additional accreditation by external agencies, including the College of American Pathologists (CAP), and some states may have their own certification processes which are more stringent than CLIA. CLIA and the accrediting agencies only evaluate the laboratory, not the specific components of each test. “CLIA testing” is often used to distinguish between clinical testing, which requires specific validation, compliance, and safety measures due to the required laboratory certifications, and testing that is not subject to the same standards and thus not appropriate for medical use.

Consumer-/Client-Initiated Testing: Genomic testing requested by an individual. This is often used to describe DTC testing, but can also fall under physician-mediated and healthcare provider-ordered testing (Moyer, 2019).

Direct-to-Consumer (DTC) Genetic/Genomic Testing: Genomic testing offered directly to an individual without requiring a referral or order from a healthcare provider (Bollinger, Green, & Kaufman; Foster & Sharp, 2008; Turrini & Prainsack, 2016).

Elective Genomic Testing: Genomic testing ordered in the absence of a medical indication ("Elective genetic and genomic testing" 2021) to detect health risks, ancestry, or trait information. There is no single best term and overlap exists between the

meanings of other terms that are used, which include preventive, proactive, and consumer-initiated genomic testing, and genomic screening (Lu et al., 2019). For this paper, we consistently use elective genomic testing.

Food and Drug Administration (FDA) Regulation: The FDA has the authority to regulate laboratory-developed tests (LDTs), including genomic tests, under their enforcement discretion policy (Administration, 2018). Most genetic tests are not currently regulated, although some are (Administration, 2017; Food and Drug Administration, 2019; Hayden, 2017).

Healthcare Provider-/Physician-Ordered Genetic/Genomic Testing: Genomic testing ordered by a healthcare provider after an in-person or telemedicine visit.

Indication-Based/Diagnostic Testing: Genomic testing performed due to a presenting phenotype in the proband and/or family (Biesecker & Green, 2014).

Manual Interpretation vs. automated interpretation vs. no-interpretation: Genomic test results can be interpreted by a genetics professional, annotated based on public genetic databases without review, or not annotated at all, including results returned as raw data only.

Medically actionable: A genomic result that has guidelines-based screening, management, or treatment options available that reduce morbidity or mortality (Miller et al., 2021).

Physician-Mediated Genetic/Genomic Testing: Genomic testing offered directly to an individual in which the company or laboratory provides access to a physician to order the testing and, to some extent, review the individual's medical history (Stoll, 2020).

Third party interpretation services: Databases that allow participants to enter their raw data into a database, which provides additional information about their genetic variations (Badalato, Kalokairinou, & Borry, 2017; Wang et al., 2018). These databases are typically not regulated by CLIA and the results are not reviewed by a qualified or licensed healthcare provider.

Supplemental Document 2. Additional considerations for EGT.

Testing methodologies common in EGT

EGT testing methodology typically employs either a genotyping or a sequencing approach for identifying reportable variation. Genotyping can be performed by various assays such as SNP arrays or using sequencing techniques. Some labs offer array-based testing, which is able to detect variants associated with risk for specific conditions or traits. Depending on the design of the array, this testing can uncover copy number variants (CNVs), monogenic disease risks, carrier findings, PGx results, polygenic risk score information as well as trait and ancestry information. It is important to note that arrays can provide a tremendous amount of useful information, yet there are limitations. Array accuracy is typically lower than that for sequencing, with rare variants especially performing poorly; recent studies have demonstrated false positive results among rare

pathogenic and likely pathogenic variants 45-84% of the time (Blout Zawatsky et al., 2021; Weedon et al., 2021). Unless the probes on the array were specifically designed and validated before assay launch, array results for rare variants should be confirmed with an orthogonal test. In addition to false positive findings, array based testing will miss variants that are not included in the array design (false negative findings), as one study found this occurred in 72% of samples that were also sequenced (Blout Zawatsky et al., 2021). For example, an individual may have a pathogenic/likely pathogenic (P/LP) monogenic variant that is not included on the array and therefore may receive false reassurance from a negative report. These array design variations can result in getting different results from different laboratories. In addition, some types of genetic testing, like PRSs, are known to have significant differences in predictive value depending on the ancestry/race of the individual (Wand et al., 2021; Wang et al., 2021). PRS prediction accuracy can also be limited by the sample size of the GWAS used to generate the PRS, and the extent to which the trait in question is heritable to begin with (Cross-Disorder Group of the Psychiatric Genomics et al., 2013). The clinical utility of PRS predictions is limited by the difficulty in translating relative risks for a population to absolute risks of disease for the individual, and by the superiority of traditional risk calculators for chronic disease (due to the inclusion of multiple risk factors). Their utility may also be limited in unselected populations (Lewis & Vassos, 2020).

Elective testing can also be performed using next generation sequencing (NGS) technologies. NGS testing can range from limited gene panels to whole genome (WGS) or exome sequencing (WES). Results from this type of testing can provide the same type of information detectable by array testing and far more, dependent upon test

validation. In some cases, however, array testing may be able to detect variants not detected by NGS depending on test validation differences. For example, while it is technically feasible to detect copy number variations using NGS, the laboratory may not be using validated CNV detection algorithms or may not have included these detection methods in the bioinformatics pipeline. It is important to note that many laboratories utilize WES/WGS, but may limit analysis or results to certain genes, as compared to an NGS assay designed to only sequence a specific subset of genes. Analysis may be further limited to a specific subset of disease risks associated with a gene, as many genes have multiple associated conditions (e.g., *BRCA2* and association with Hereditary Breast and Ovarian Cancer syndrome as well as autosomal recessive Fanconi anemia). Some laboratories will claim to offer results spanning the entire interpretable genome or exome. In these cases, individuals could learn information about monogenic disease risk, carrier status, risk alleles, PGx information, PRSs, information about non-medical traits, ancestry and more. Technologies such as polymerase chain reaction (PCR)-based assays and methylation testing are not commonly used for EGT given they are typically designed for specific disorders or variants. This landscape will evolve over time as new methodologies are developed and become commercially available.

Different methodologies and different assays will also vary in the thoroughness or completeness of the assay for detecting variation associated with specific conditions. Ideally, a well-designed test should cover all clinically relevant regions and variants associated with the diseases offered in the EGT. If a given testing technology cannot or does not cover commonly encountered pathogenic variants for the condition (e.g., an

exome test may not cover commonly seen pathogenic intronic variants), it is important to ascertain whether those regions are tested using complementary methods. Analytical validity of the genetic test may be able to be assessed via request of a sample report and review of its methodology. The assay and technology used should be noted, as well as which variant types are included in testing (e.g., CNVs, other structural variants) and at what resolution (e.g., single exon deletion). Elective genomic test sequencing technologies are less likely than indication-based tests to offer completeness of coverage though the entire clinical region of interest, as filling in missing data by orthogonal methods (e.g. Sanger sequencing of results identified through NGS) is costly. For NGS assays, laboratories should therefore disclose a) general coverage expectations (e.g. validation studies that show that generally, >95% of the clinical region is covered at $\geq$20X) and b) critical regions where the assay underperforms or coverage cannot be guaranteed in the majority of samples (e.g. regions of high homology, such as *PMS2* where a supplemental assay is typically out of scope for low-cost testing). The latter is critical to help the clinician modify the interpretation of a negative result (e.g. the negative predictive value of a negative result for genes associated with a particular disorder may be significantly reduced when parts of genes with high detection rates are not covered). Point B is also critical for positive results, as false positive variants due to the presence of a pseudogene may be reported. Alternatively, it is possible to assess general performance with regard to completeness of coverage if the lab is willing to disclose gene-based performance statistics.

File types commonly available in EGT

Some laboratories offering EGT may offer the client the raw data from their genetic testing results, typically for free. The raw data file type available for sharing depends on the technology used to generate the test results, and the processing step in the bioinformatics pipeline from which the results are shared. In the case of sequencing, raw sequencing reads are stored in .fastq or .ubam files, which are then aligned to a specific genome build in .bam or .cram files (Clarke et al., 2012; Cock et al., 2010; Crawford, Cooke Bailey, & Briggs, 2019). Variants identified in a specific individual are stored in .vcf files. A laboratory may also provide information on site-level coverage in a .gvcf file. There is some loss and prioritization of information at some steps of processing the raw genetic data, which leads to reduced and thus more manageable file sizes for storing and sharing. However, discarded data typically can't be inferred from downstream data. For example, the drawback to acquiring solely .vcf files is that should there be improvements in variant calling algorithms after the results are shared, it will not be possible to infer more accurate calls without the upstream .fastq or .bam files. In the case of genotyping data, typically a .vcf or equivalent .txt file is provided that includes all sites probed on the array and the corresponding genotypes of the individual, including homozygous reference calls. This is the data type commonly uploaded to third party interpretation services on the internet.

Supplemental Document 3: Evaluation of laboratories and their test offerings:

Evaluating laboratories offering EGT:

Test cost and turnaround time should be readily available. Test cost may not be transparent for EGT. For example, raw data release, updated reports, and counseling

services may not be included in the initial test cost, so clarification of included services is necessary.

Other indications of quality laboratories are much the same as with typical genetic testing, including labs submitting information to ClinVar (Landrum et al., 2016; Landrum et al., 2018) and other academic contributions such as publishing data on genotype/phenotype performance or detection rates.

Language to assist with evaluation of laboratories and their test offerings:

We recommend requesting a sample report of the specific test under evaluation, or additional materials (white papers, publications) regarding the methodology of the test. The following is intended to guide evaluation of these characteristics while providing specific language that can be used to speak with a laboratory director or other genomic specialist regarding key characteristics of EGT which may not be readily available.

General test information

- Test cost and turnaround time (TAT)
- Was this test designed for non-indication (no phenotype; general untargeted screen) purposes or diagnostic purposes?

Licenses, certifications, and accreditations

- CLIA certification and CAP accreditation, state-specific approvals (e.g. NYS)
    - Request sample report – CLIA/CAP # should be listed along with the lab director.

    - Note that the laboratory offering the test may not carry out all parts. It is increasingly common that one or more processes are outsourced to other entities. The laboratory that signs the clinical report should include such information in the methodology section. Note that the final result can only be considered “CLIA grade” if all steps along the way were carried out by a CLIA-certified entity. Ask:
        - Does the laboratory carry out all steps in house?
        - If not, which parts of the test are outsourced and to whom?
        - What are the CLIA/CAP IDs of additional entities performing part/s of the test?

Methodology and sample report

- Assay used (e.g. WES, WGS, array)
    - Are Copy Number Variants (CNVs) detected? If so, at what resolution (single exon)?
- Does the lab have white papers or published analytical validation of the test? If not, are there test info sheets/statistics on their website and how informative are they?
    - Has the lab validated the assay’s ability to detect specific prevalent pathogenic variants that are known to be challenging?
    - How many tests have been processed? (Note: most labs may not share exact numbers)?

    - What are the detection rates for (Gene/Group of genes) and how do they compare to published detection rates? (e.g. for ACMG secondary finding genes)
        - This will provide indirect insight into the lab's curation/classification quality. If detection rates are a lot higher than expected the root case is often low quality of variant curation. This may vary by population.
    - What % of the tests processed meet the published TAT?
        - Laboratories are required to track this under CAP – though most won't disclose to customers.
    - For tests where only likely pathogenic/pathogenic variants are reported: Are VUSs available upon request?
        - Use caution if requesting, it may be of value to ask whether the VUS has gone through the full interpretation process, confirmations, etc. As always, VUS should be interpreted with caution.

Test design, clinical utility, and validity

- Does the laboratory adhere to ACMG standards with regard to gene content (e.g., limit genes of uncertain significance aka GUSes) and can they share inclusion criteria?
    - How do they select genes to be included on this test?
- Clinical regions of interest (ROI)?

    - Does the test interrogate the entire coding sequence for all included genes (note: some genes have difficult to sequence regions and these may be omitted for cost reasons in an elective test).
    - Is the test designed to cover prevalent pathogenic variants that are outside the “standard” ROI (i.e. coding exons +/- short intronic flanks)?
- What are the variant filtering criteria? If using allele frequency (AF) filters, are there exceptions? (e.g., >5% AF filtered out, but a set list of founder variants of high frequency are reported if detected)

Does the lab share a sample report on their website or were you able to request one? If so, review the methodology section (which should provide much of the below):

- Appropriate coverage of the genes included:
    - Are technically challenging genes covered (e.g., genes with high homology such as *PMS2*)?
    - Does the lab ensure completeness of coverage for all listed genes?
    - If completeness is not guaranteed, does the lab disclose insufficiently covered genes on the report (both: regions that are always excluded, this would be in the methods section of the report, and regions that failed in a given patient-those would be in the body of the report)?
    - Note: Because EGTs often need to be paid out of pocket, completeness of coverage is often not guaranteed due to the high cost associated with (Sanger) fill-in sequencing.

    - Does the lab have coverage performance statistics by gene (so one can gauge likelihood of getting high quality results when completeness of coverage is not guaranteed)?
- Analytical validation: labs are required to list analytical performance on the report but numbers can be misleading.
- Analytical sensitivity and specificity: does the lab list 95% Confidence Intervals? This reveals the depth of their validation (i.e., the # of samples used).
    - Is analytical performance listed by variant type (SNVs, in/dels, CNVs) and are confidence intervals provided (how many variants were included per variant type)?
- Does the lab confirm ALL reported variants prior to reporting (SNVs, indels, CNVs)?
    - How do they confirm the variant? (e.g., Sanger, second Next generation Sequencing (NGS) technique, multiplex-ligation dependent probe amplification (MLPA), etc.)
    - What criteria must be met if a variant is reported without confirmation (e.g., minimum quality score, read depth, variant type, etc.)? This is usually not provided on the report but should be available upon request.
- How are variants classified?
    - Does the laboratory use up to date variant interpretation standards? For example, ACMG/AMP guidelines, ClinGen gene/disease specific adaptations of the original ACMG guideline, or other standardized methods from reputable sources? Note: The original ACMG/AMP

classification guideline (Richards, 2015) is inferior to ClinGen's gene-disease specific adaptations.

    - When using databases, how often is the pipeline updated with the databases? (e.g., pulls new ClinVar updates quarterly vs. annually)
    - If automated, is the reported classification pulled from a database (i.e., ClinVar)? Is this reviewed by a board-certified geneticist prior to reporting?
- Are results interpreted by qualified professionals vs. automated interpretation vs. is just raw data provided to interpret your own data?
    - Variant calling, curation, and reporting criteria (variant scientist involvement preferable)
        - Ask lab for specifics: Is there a curation team in place or does the lab director who signs the report do it? If yes, what are their qualifications (may also want to ask where the curators are located, some labs use offshore teams and in that case it may be important to dig further)?
- Does the lab submit variants to ClinVar?
    - Can check list of submitters and #s submitted on ClinVar website.

Data Storage

- What is the raw data file format (.bam, .vcf, or other type of file) and is it available upon request?
    - How do you request raw data? Who is able to request the data?
- How long is the biological sample or extracted DNA stored for? How long is the raw data stored for?

- Who has access to the data? What level of access do third parties receive, if any?
- Is it possible to ask for a sample to be destroyed? If so, how?

If a sample is destroyed, do third parties also have their access to the sample removed?

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