Multigene Panel Testing in Oncology Practice
How Should We Respond?

A great success of modern human genetics is the identification of specific genes that, when altered, confer clinically recognized traits, such as cancer susceptibility, and enable predictive genetic testing. In past decades, cost and turn-around time limited cancer genetic risk assessment, and it was rarely feasible to test a patient for more than 1 well-defined condition (eg, hereditary breast ovarian cancer [HBOC] or Lynch syndrome). Transformative sequencing advances now permit massively parallel, rapid analysis of many genes, making the "$1000 genome" an imminent reality. In June 2013, long-term barriers to cancer genetic testing were breached by a remarkable convergence of events: the disclosure of her BRCA1 mutation by the actress Angelina Jolie, which dramatically increased public awareness and demand for genetic testing; and the US Supreme Court decision against gene patenting, which allowed competition to reduce the price of BRCA1 and BRCA2 (BRCA1/2) testing. Incentives quickly shifted toward sequencing more genes as laboratories competed to offer panels of increasing numbers of genes (from 6 to >100) at decreasing prices. Perhaps because testing costs have fallen so greatly, insurers rarely object to multigene panels as a means of diagnosing recognized syndromes (eg, HBOC) when relevant guidelines are met. However, most payers will not cover more than 1 cancer risk assessment test, creating an incentive to sequence any genes of interest concurrently rather than sequentially. In short, multigene panels have entered the clinic, and there seems little chance of forcing the genie back into the bottle.

Fortunately, multigene panels offer significant benefits over sequential single-gene testing. They are cheaper, faster, and more efficient for differential diagnosis. Most important, they may identify deleterious mutations that the pedigree would not suggest, particularly for families with cancer patterns that deviate from recognized syndromes. These advances come with drawbacks, however, related to the lack of a testing track record for many genes on commercially available panels. Panel testing is complicated by 3 levels of uncertainty about mutations in less widely tested genes, regarding (1) the magnitude of cancer risk (penetrance), (2) the anatomical and age-specific scope of cancer risk, and (3) the clinical relevance of missense variants in genes for which the spectrum of normalcy is poorly defined. Variants of uncertain significance (VUS) increase in frequency with the number of genes sequenced, and, if skilled genetic counseling is not provided, this may cause anxiety and unwarranted interventions. Recently, concerns have arisen that technical advances in genomics have outpaced our ability to provide safe, ethical care. When guided by appropriate expertise and in conjunction with clinical research, however, multigene panels offer substantial opportunities to improve cancer risk assessment, early detection, and prevention.

Ideally, a new test would enter patient care only after all essential questions about its interpretation were answered. Instead, we must now evaluate multigene panel testing in medias res. Our recommendations for next steps include research, referral, and training.

Well-designed studies are crucial to determine the clinical and societal value of multigene panel testing. Studies must evaluate cancer causation associated with mutations in unfamiliar genes (eg, BRIP1, RAD51D), particularly among families not meeting traditional syndromic criteria; must elucidate mutation prevalence and penetrance, and the anatomic, pathologic, and prognostic characteristics of associated cancers; and must evaluate panel testing’s impact on the uptake and outcomes of screening and prophylactic procedures. High-priority topics include the effectiveness of clinician-patient communication and the health care delivery systems required for panel testing, with consideration of access and ethics; and the cost-effectiveness of a multigene panel vs sequential single-gene testing strategy. We urgently need a bioinformatics infrastructure for data sharing, rapid VUS reclassification, and active case-finding of mutation carriers’ at-risk relatives: such infrastructure will be mandatory for consideration of whole-genome sequencing in routine practice. The Table presents a proposed research agenda.

The exponential growth in data volume and complexity strains existing counseling models, which entail discussion of gene-specific cancer risks and evidence-based interventions for well-studied syndromes. Clinicians face new and difficult questions:

• For which patients is a multigene panel indicated instead of a single-gene test?
• For which patients will insurance cover a multigene panel?
• Which panel should be used: high-penetration (5-6 genes), tumor site-specific (15-20), or broader (25-100)?
• Should patients be counseled about the specific risks of each gene before testing?
• How to manage mutations inconsistent with family history (eg, CDH1, no gastric cancer)?
• Should relatives be offered testing for mutations of uncertain penetrance (eg, CHEK2)?
• How should patients be counseled about VUS, given their high rate with multigene panels?
• Should less familiar mutations be managed similarly to recognized syndromes (eg, screening breast mag-
netic resonance imaging for PALB2 as for BRCA1/2 mutation carriers)?

Proposed modifications to the clinician-patient encounter, including a streamlined counseling approach guided by clinical relevance, are being tested in important clinical trials.7

Amid this uncertainty, a point of clarity emerges: that expertise in cancer genetics, always endorsed by the American Society of Clinical Oncology, National Comprehensive Cancer Network, and others,4 is more critical now than ever before. We recommend referral to expert clinicians for test selection, pretest and posttest counseling whenever possible. The existing workforce is insufficient, and thus we urge a societal investment in training for genomics and precision medicine, both of genetic counselors and of interested physicians. The growing accessibility of genomic sequencing has a dazzling potential to transform oncology and medicine. However, the imperative to do no harm mandates that we exercise careful judgment in (1) the patients we select for multigene panel testing; (2) the number and identity of genes we sequence, with custom gene selection a rational alternative to prefabricated panels; and (3) the cancer screening and prevention strategies we advise.

Practice guidelines are evolving with emerging evidence, but it is important to maintain a clear separation between routine care and research, particularly for comprehensive strategies such as whole-genome sequencing. Patient care should be guided by the family cancer history when a less-studied mutation is detected, and participation in well-designed trials of testing, communication, and intervention strategies (Table) should be strongly encouraged.

### Table. Proposed Research Agenda for Multiple-Gene Panel Testing

<table>
<thead>
<tr>
<th>Research Topic</th>
<th>Desired Study Characteristics</th>
<th>Data Resources and Ongoing Studies</th>
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<tbody>
<tr>
<td>Gene-Specific Mutation Prevalence, Penetration, and Cancer Prognosis</td>
<td>Racially/ethnically diverse cancer cases, well-curated family history data</td>
<td>Breast and Colon Cancer Family Registries,4 National Cancer Institute Cohort Consortiumb</td>
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<tr>
<td>Carrier frequency in the general population</td>
<td>Population-based cases and controls</td>
<td>Breast and Colon Cancer Family Registries,4 National Cancer Institute Cohort Consortiumb</td>
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<td>Penetration, including sources of heterogeneity in risk</td>
<td>Kin-cohort or case-control designs</td>
<td>Breast and Colon Cancer Family Registries,4 National Cancer Institute Cohort Consortiumb</td>
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<td>Anatomic, pathologic, prognostic spectrum of cancers</td>
<td>Clinically annotated data sets with germline sequencing results</td>
<td>PROMPT Study*</td>
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<td>Reclassifying variants of uncertain significance</td>
<td>Data sharing and bioinformatics infrastructure</td>
<td>PROMPT Study*, ENIGMA Consortium,4 InSiGHT Group4</td>
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<td>Evaluation of cancer causation by mutations</td>
<td>Functional studies; tumor profiling and loss of heterozygosity studies; segregation analyses and other family-based designs</td>
<td>Translational research studies needed</td>
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### Clinical Approaches and Cost-Effectiveness

| Approaches to genetic counseling and informed consent | Clinical trials | COGENT,4 METER, RESPECT studies |
| Uptake and outcomes of cancer screening and prevention | Prospective studies of clinical and patient-reported outcomes | USC/Stanford Cancer Genetics Hereditary Panel Study4, PROMPT Study4 |
| Patient-reported preferences and outcomes | Prospective studies of clinical and patient-reported outcomes | USC/Stanford Cancer Genetics Hereditary Panel Study; Memorial Sloan-Kettering Study of Multiplex Testing5, PROMPT,4 METER, RESPECT studies |
| Incremental benefit of analyzing more vs fewer genes | Clinical studies of testing options, including whole-genome sequencing | Cancer-focused prospective studies needed |
| Cost-effectiveness of panel vs single-gene testing | Simulation model-based analyses | To be informed by results of the studies listed here |

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#### REFERENCES