The impact of hereditary cancer gene panels on clinical care and lessons learned

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Abstract Mutations in hereditary cancer syndromes account for a modest fraction of all cancers; however, identifying patients with these germline mutations offers tremendous health benefits to both patients and their family members. There are about 60 genes that confer a high lifetime risk of specific cancers, and this information can be used to tailor prevention, surveillance, and treatment. With advances in next-generation sequencing technologies and the elimination of gene patents for evaluating genetic information, we are now able to analyze multiple genes simultaneously, leading to the widespread clinical use of gene panels for germline cancer testing. Over the last 4 years since these panels were introduced, we have learned about the diagnostic yield of testing, the expanded phenotypes of the patients with mutations, and the clinical utility of genetic testing in patients with cancer and/or without cancer but with a family history of cancer. We have also experienced challenges including the large number of variants of unknown significance (VUSs), identification of somatic mutations and need to differentiate these from germline mutations, technical issues with particular genes and mutations, insurance coverage and reimbursement issues, lack of access to data, and lack of clinical management guidelines for newer and, especially, moderate and low-penetrance genes. The lessons learned from cancer genetic testing panels are applicable to other clinical areas as well and highlight the problems to be solved as we advance genomic medicine.

Cancer is among the leading causes of morbidity and mortality worldwide. Germline mutations for monogenic, highly penetrant cancer susceptibility genes are observed in 5%–10% of all cancers (Lu et al. 2014), and many solid organ cancers have clinical guidelines for evaluation and genetic counseling/testing (Hampel et al. 2015; Robson et al. 2015). Hereditary cancers due to monogenic causes are characterized by earlier age of onset, other associated cancers, and often a family history of specific cancers or associated features. It is clinically important to recognize these individuals and their family members to guide clinical management for those with cancer (Hennessy et al. 2010; Ledermann et al. 2014; Pennington et al. 2014; Kurian et al. 2017) and to identify at-risk patients who will benefit from enhanced surveillance to permit early detection and/or risk reduction measures (Kurian et al. 2010). Identification of carriers of cancer predisposition genes also enables cascade genetic testing of at-risk family members to refine risk and identify both high and average risk family members, tailor care to improve outcomes, and more efficiently use health-care resources.
Cancers have long been recognized to run in certain families. Because of the expense to Sanger sequence hereditary cancer genes such as BRCA1/2 or mismatch repair genes in Lynch syndrome, genetic testing guidelines were developed 10–15 years ago for many common cancers to identify patients with a high probability of carrying a cancer predisposition mutation. These guidelines were incorporated into the predictors such as BRCAPro (Parmigiani et al. 1998), Amsterdam (Vasen et al. 1991), and Bethesda (Rodriguez-Bigas et al. 1997) or modified Bethesda criteria (Umar et al. 2004), which have been utilized to identify patients with a prior probability of at least 10% to carry a heritable cancer mutation. However, these criteria are not sensitive enough to identify all mutation carriers (Berry et al. 2002). For example, although several risk estimate algorithms have been developed and genetic testing for hereditary breast and ovarian cancer (HBOC) has been available for 20 years, it was estimated as of 2012 that only 30% of patients with breast cancer and 5% of asymptomatic BRCA1/2 carriers may have been identified in the United States (Drohan et al. 2012).

With the reduction in the cost of sequencing with next-generation sequencing (NGS) technologies and using elimination of patents on BRCA1/2 for diagnostic testing in June 2013, there was an immediate increase in the number of genes that could be evaluated simultaneously and in the number of laboratories that entered the market. This had the effect of decreasing the price charged from $3340 for BRCA1/2 (Myriad Genetics, Annual Report 2012) to now $250 for a panel of 30 genes (Color Genomics, 2017), increasing access to testing with more laboratories partnering with more payers, and decreasing turnaround times from 10 wk to 10–21 d to enable incorporation of genetic information with medical decision making at the time of initial cancer diagnosis. Coincident with these changes on the laboratory side, in May 2013, Angelina Jolie revealed her BRCA1 status and preventive measures she had undertaken with an op-ed in The New York Times (http://www.nytimes.com/2013/05/14/opinion/my-medical-choice.html). The associated media coverage had a significant impact on increasing the awareness of the public about hereditary cancer (Borzekowski et al. 2014; Kamenova et al. 2014; Kosenko et al. 2016).

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Panel gene testing has doubled the mutation detection rate for patients undergoing either cancer site–specific (Kapoor et al. 2015; Minion et al. 2015) or pan-cancer panels (Ricker et al. 2016; Susswein et al. 2016). As a result, panel testing has increased and become the most common testing option for cancer genetic testing (Blazer et al. 2015).

As laboratories were designing panels of genes to offer in clinical testing, there was and still is incomplete data available on the frequency, penetrance, and cancer spectrum associated with many of the heritable cancer genes, especially for those genes that had been relatively recently identified. Different panel options were constructed and offered by laboratories (Table 1). The majority of the panels included genes for specific hereditary cancer predisposition syndromes and provided various testing options for the number of genes included in the panels ranging from a small number of highly penetrant, well-established genes with NCCN (National Comprehensive Cancer Network) clinical care guidelines to larger panels including more recently identified genes with lower penetrance and/or less certainty about the age-related penetrance and associated cancers (Tables 1 and 2). Laboratories also offered pan-cancer panels covering large numbers of approximately 30 to 60 genes for patients who had family or personal histories that did not fit a single hereditary cancer syndrome. With more expansive testing, it has
Table 1. Genes causing hereditary cancer syndromes and panels in which they are included

| Gene       | Breast and gynecologic cancers | Colorectal and gastrointestinal | Pancreas | Melanoma | Prostate | Renal and urinary tract | PGL/PCC and endocrine | Pediatric | Brain | High-moderate risk and guideline | Pan-cancer |
|------------|--------------------------------|---------------------------------|----------|----------|----------|------------------------|-----------------------|-----------|-------|---------------------------------|------------|
| AIP        |                                |                                 |          |          |          |                        |                       |           |       |                                 | 0          |
| ALK        |                                |                                 |          |          |          |                        |                       |           |       |                                 | 0          |
| APC        |                                | xxxxxxxxxx                      | xxxxxxx  |          | xx       | xx         | xxx                   | xxxxxxxxxx           |           | xxx   |                                 | xxxxxx     |
| BMPR1A     |                                | xxxxxxxxxx                      | xx       |          |          |                        |                       |           | xxx   |                                 | xxxxxx     |
| BRCA1      | xxxxxxxxxxxxxxx               | xxxxxxx                         |          |          | xx       | xxx                   | xxxxxxxxxx           |           | xxx   |                                 | xxxxxx     |
| BRCA2      | xxxxxxxxxxxxxxx               | xxxxxxx                         | xxxxx    | xxx      | xxx      | xxx                   | xxxxxxxxxx           |           | xxx   |                                 | xxxxxx     |
| CDH1       | xxxxxxxxxxxxxxx               |                                 |          |          |          |                        | xxxxxxxxxx           |           | xxx   |                                 | xxxxxx     |
| CDK4       |                                |                                 |          |          |          |                        | xxxxxxxxxx           |           | xxx   |                                 | xxxxxx     |
| CDKN2A     | xxxxxxx                      | xxxxxxx                         |          |          |          |                        | xxxxxxxxxx           |           | xxx   |                                 | xxxxxx     |
| EPCAM      | xxxxxxxxxxx                   | xxxxxxxxxxx                    | xxxxxxx  | xxx       | xxx      | xxx                   | xxxxxxxxxx           |           | xxx   |                                 | xxxxxx     |
| FH         |                                | xxxxxxx                         | xxxxxxx  |          | xx       |                        | xxx                   |           | xxx   |                                 | xxxxxx     |
| FLCN       |                                | x                               |          |          |          |                        | xxx                   |           | xxx   |                                 | xxxxxx     |
| MEN1       | x                             | xx                             |          |          |          |                        | xxxxxxxxxx           |           | xxx   |                                 | xxxxxx     |
| MET        |                                | xxxxxxx                         |          |          |          |                        | xxx                   |           | xxx   |                                 | xxxxxx     |
| MLH1       | xxxxxxxxxxx                   | xxxxxxxxxxx                    | xxxxxxx  | xxx       | xx       | xxx                   | xxxxxxxxxx           |           | xxx   |                                 | xxxxxx     |
| MSH2       | xxxxxxxxxxx                   | xxxxxxxxxxx                    | xxxxxxx  | xxx       | xx       | xxx                   | xxxxxxxxxx           |           | xxx   |                                 | xxxxxx     |
| MSH6       | xxxxxxxxxxx                   | xxxxxxxxxxx                    | xxxxxxx  | xxx       | xx       | xxx                   | xxxxxxxxxx           |           | xxx   |                                 | xxxxxx     |
| MUTYH      | xxxxxx                       | xxxxxxx                        |          |          |          |                        | xxx                   |           | xxx   |                                 | xxxxxx     |
| NF1        | xxxxxx                       | xx                             |          |          | xx       |                        | xxxxxxxxxx           |           | xxx   |                                 | xxxxxx     |
| NF2        |                                |                                 |          |          |          |                        | xxxxxxxxxx           |           | xxx   |                                 | xxxxxx     |
| PALB2      | xxxxxxxxxxx                   | xxxxxxx                        | xx       | x        |          |                        | xxxxxxxxxx           |           | xxx   |                                 | xxxxxx     |
| PMS2       | xxxxxxx                      | xxxxxxxxxxx                    | xxxxxxx  | xxx       | xx       | xxx                   | xxxxxxxxxx           |           | xxx   |                                 | xxxxxx     |
| PTCH1      |                                |                                 |          |          |          |                        | xxx                   |           | xxx   |                                 | xxxxxx     |
| PTEN       | xxxxxxxxxxx                   | xxxxxxx                        | xxxxxxx  | xxx       | xx       | xxx                   | xxxxxxxxxx           |           | xxx   |                                 | xxxxxx     |
| RB1        |                                |                                 | xxxxxxx  | xxx       | xx       | xxx                   | xxxxxxxxxx           |           | xxx   |                                 | xxxxxx     |
| RET        |                                |                                 |          |          |          |                        | xxxxxxxxxx           |           | xxx   |                                 | xxxxxx     |
| SDHB       | xx                           | xx                             | xxxxxxx  | xxx       | xx       |                        | xxx                   |           | xxx   |                                 | xxxxxx     |
| SDHD       | xx                           | xx                             | xxxxxxx  | xxx       | xx       |                        | xxx                   |           | xxx   |                                 | xxxxxx     |
| SMAD4      | xxxxxxxxxxx                   | xx                             |          |          |          |                        | xxx                   |           | xxx   |                                 | xxxxxx     |
| STK11      | xxxxxxxxxxx                   | xxxxxxx                        |          |          |          |                        | xxx                   |           | xxx   |                                 | xxxxxx     |
| TP53       | xxxxxxxxxxxxxxxxxxx          | xxxxxxxxxxx                    | xxxxxxx  | xxx       | xxx      | xxx                   | xxxxxxxxxx           |           | xxx   |                                 | xxxxxx     |
| TSC1       | xx                           | xxxxxxx                        |          |          |          |                        | xxx                   |           | xxx   |                                 | xxxxxx     |

Genes with established high risk/penetrance for at least one cancer site

AIP xx
ALK xx xxx xxx
APC xxxxxxxxxx xxxxxxx
BMPR1A xxxxxxxxxx xx
BRCA1 xxxxxxxxxxxxxxx xxxxxxx x xxx
BRCA2 xxxxxxxxxxxxxxx xxxxxxx xxx xxx xxx xxxxxxx
CDH1 xxxxxxxxxxxxxx xxxxxxxxxx
CDK4 xxxxxxxxxx
CDKN2A xxxxxxxxxx x x xxxxxxx
EPCAM xxxxxxxxxxx xxxxxxxxxxx xxxxxxx xxxxxxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx ...)
| Gene   | Breast and gynecologic cancers | Colorectal and gastrointestinal | Pancreas | Melanoma | Prostate | Renal and urinary tract | PGL/PCC and endocrine | Pediatric | Brain | High–moderate risk and guideline | Pan-cancer |
|--------|--------------------------------|---------------------------------|----------|----------|----------|------------------------|-----------------------|-----------|-------|---------------------------------|------------|
| TSC2   |                                |                                 | xxx      | xxx      | xxx      | xxx                    | xxx                   | xxx       | xxx   | xxx                            |           |
| VHL    |                                |                                 | xxx      | xxx      | xxx      | xxx                    | xxx                   | xxx       | xxx   | xxx                            |           |
| WT1    |                                |                                 | xx       | xx       | xx       | xx                     | xx                    | xx        | xxx   | xxx                            |           |

**Genes with moderate risk/penetrance**

| Gene   | Breast and gynecologic cancers | Colorectal and gastrointestinal | Pancreas | Melanoma | Prostate | Renal and urinary tract | PGL/PCC and endocrine | Pediatric | Brain | High–moderate risk and guideline | Pan-cancer |
|--------|--------------------------------|---------------------------------|----------|----------|----------|------------------------|-----------------------|-----------|-------|---------------------------------|------------|
| ATM    | x xxx xxx xxx xxx             | xxx xxx xxx xxx                | xxx      | xxx      | xxx      | xxx                    | xxx                   | xxx       | xxx   | xxx                            |           |
| BRIP1  | xxx xxx xxx xxx              | xxx xxx xxx xxx                | xxx      | xxx      | xxx      | xxx                    | xxx                   | xxx       | xxx   | xxx                            |           |
| CHEK2  | xxx xxx xxx xxx              | xxx xxx xxx xxx                | xxx      | xxx      | xxx      | xxx                    | xxx                   | xxx       | xxx   | xxx                            |           |
| RAD51C | xxx xxx xxx xxx             | xxx xxx xxx xxx                | xxx      | xxx      | xxx      | xxx                    | xxx                   | xxx       | xxx   | xxx                            |           |
| RAD51D | xxx xxx xxx xxx             | xxx xxx xxx xxx                | xxx      | xxx      | xxx      | xxx                    | xxx                   | xxx       | xxx   | xxx                            |           |

**Genes with low risk/penetrance or newly identified with unknown risk/penetrance**

| Gene   | Breast and gynecologic cancers | Colorectal and gastrointestinal | Pancreas | Melanoma | Prostate | Renal and urinary tract | PGL/PCC and endocrine | Pediatric | Brain | High–moderate risk and guideline | Pan-cancer |
|--------|--------------------------------|---------------------------------|----------|----------|----------|------------------------|-----------------------|-----------|-------|---------------------------------|------------|
| AXIN2  | xxx                           | xxx xx xxx xxx xxx             | xxx      | xxx      | xxx      | xxx                    | xxx                   | xxx       | xxx   | xxx                            |           |
| BAP1   | xxx                           | xxx xxx xxx xxx                | xxx      | xxx      | xxx      | xxx                    | xxx                   | xxx       | xxx   | xxx                            |           |
| BARD1  | xxx xxx xxx xxx             | xxx xxx xxx xxx                | xxx      | xxx      | xxx      | xxx                    | xxx                   | xxx       | xxx   | xxx                            |           |
| BLM    | xxx                           | xxx xxx xxx xxx                | xxx      | xxx      | xxx      | xxx                    | xxx                   | xxx       | xxx   | xxx                            |           |
| GALNT12| xxx                           | xxx xxx xxx xxx                | xxx      | xxx      | xxx      | xxx                    | xxx                   | xxx       | xxx   | xxx                            |           |
| GREM1  | xxx                           | xxx xxx xxx xxx                | xxx      | xxx      | xxx      | xxx                    | xxx                   | xxx       | xxx   | xxx                            |           |
| HOXB13 | xxx                           | xxx xxx xxx xxx                | xxx      | xxx      | xxx      | xxx                    | xxx                   | xxx       | xxx   | xxx                            |           |
| MAX    | xxx                           | xxx xxx xxx xxx                | xxx      | xxx      | xxx      | xxx                    | xxx                   | xxx       | xxx   | xxx                            |           |
| MITF   | xxx                           | xxx xxx xxx xxx                | xxx      | xxx      | xxx      | xxx                    | xxx                   | xxx       | xxx   | xxx                            |           |
| MRE11  | xxx xxx xxx xxx             | xxx xxx xxx xxx                | xxx      | xxx      | xxx      | xxx                    | xxx                   | xxx       | xxx   | xxx                            |           |
| NBN    | xxx xxx xxx xxx             | xxx xxx xxx xxx                | xxx      | xxx      | xxx      | xxx                    | xxx                   | xxx       | xxx   | xxx                            |           |
| POLE D | xxx                           | xxx xxx xxx xxx                | xxx      | xxx      | xxx      | xxx                    | xxx                   | xxx       | xxx   | xxx                            |           |
| POLE   | xxx                           | xxx xxx xxx xxx                | xxx      | xxx      | xxx      | xxx                    | xxx                   | xxx       | xxx   | xxx                            |           |
| RAD50  | xxx                           | xxx xxx xxx xxx                | xxx      | xxx      | xxx      | xxx                    | xxx                   | xxx       | xxx   | xxx                            |           |
| SDHA   | xxx                           | xxx xxx xxx xxx                | xxx      | xxx      | xxx      | xxx                    | xxx                   | xxx       | xxx   | xxx                            |           |
| SDHAF2 | xxx                           | xxx xxx xxx xxx                | xxx      | xxx      | xxx      | xxx                    | xxx                   | xxx       | xxx   | xxx                            |           |
| SDHC   | xxx                           | xxx xxx xxx xxx                | xxx      | xxx      | xxx      | xxx                    | xxx                   | xxx       | xxx   | xxx                            |           |
| TMEM127| xxx                           | xxx xxx xxx xxx                | xxx      | xxx      | xxx      | xxx                    | xxx                   | xxx       | xxx   | xxx                            |           |
| XRCC2  | xxx                           | xxx xxx xxx xxx                | xxx      | xxx      | xxx      | xxx                    | xxx                   | xxx       | xxx   | xxx                            |           |

Number of xs represents how many times a gene is offered in different panel options by nine laboratories in the United States: Ambry Genetics, ARUP Lab, Color Genomics, Counsyl, Fulgent Diagnostics, GeneDx, Invitae, Myriad Genetics, and Pathway Genomics. Color Genomics and Pathway Genomics offer only one and two panels, respectively. Some genes are not included in this list and only the most expansive panel of every laboratory is included for a given syndrome. When there is a separate high/moderate risk panel offered it is included in the “High–moderate risk and guideline” section.

The risks of these genes are based on experience with childhood-associated syndromes.
| Gene       | Breast cancer | Ovarian cancer | Endometrial cancer | Colorectal cancer | Gastric cancer | Pancreas cancer | Hepatobiliary cancer | Intestinal cancer | Melanoma | Prostate cancer | Renal and urinary tract cancer | PGL/PCC and endocrine | Brain tumors | Others |
|------------|---------------|----------------|-------------------|------------------|--------------|----------------|--------------------|------------------|----------|----------------|-----------------------------------|------------------------|-------------|--------|
| APC        | 93–100%       | <1%            |                   | 1%–2%            | 4%–12%       | 2% (thyroid)  | ↑                  |                  |          |                | 15%–20%                           |                        |             |        |
| BMPR1A     | 40%–50%       | 21%            |                   |                  |              |                |                    |                  |          |                | 15%–34% (Wilms tum)               |                        |             |        |
| BRCA1      | 57–87%        | 24–54%         | 1%–2%             | ↑                | 15%–20%      |                 |                    |                  |          |                |                                   |                        |             |        |
| BRCA2      | 41–84%        | 11–27%         | 5%–7%             | ↑                |            |                 |                    |                  |          |                |                                   |                        |             |        |
| CDH1       | 39–52%        | 63–83%         | 17%–25%           | 28%–76%          |              |                |                    |                  |          |                |                                   |                        |             |        |
| CDKN2A     | ↑             | 12%–55%        | 52%–75%           | ↑                | ↑            | ↑               | ↑                  |                  | ↑        | ↑              | 95% (endocrine)                  |                        |             |        |
| EPCAM      | ↑             |↑12%–55%        | 52%–75%           | ↑                | ↑            | ↑               | ↑                  | ↑                | ↑        | ↑              |                                   |                        |             |        |
| MEND       |               |                |                   |                  |              |                |                    |                  |          |                |                                   |                        |             |        |
| MLH1       | 4%–24%        | 25%–60%        | 52%–82%           | 6%–13%           | 1%–6%        | 1%–4%          | 3%–6%             | ↑                | 1%–7%   | 1%–3%          | 1%–9% (sebaceous tm)             |                        |             |        |
| MSH2       | 4%–24%        | 25%–60%        | 52%–82%           | 6%–13%           | 1%–6%        | 1%–4%          | 3%–6%             | ↑                | 1%–10%  | 1%–3%          | 1%–9% (sebaceous tm)             |                        |             |        |
| MSH6       | 1%–11%        | 16%–26%        | 10%–22%           | <3%              | ↑            | ↑               | ↑                  | ↑                | ↑        |                |                                   |                        |             |        |
| MUTYH      | 1.5-fold      | 80%            | ↑                 |                 |              | 4%             |                    |                  |          |                |                                   |                        |             |        |
| NF1        | 8.4% by age 50|                |                   |                 |              |                |                    |                  |          |                | 1%–13%        2%–3% 15% (optic nerve gliomas); 6%–13% (peripheral nerve sheath tm) |                        |             |        |
| PALB2      | 33%–58%       | ↑              | ↑                 | ↑                |              |                |                    |                  |          |                | 40% (Wilms tum)                  |                        |             |        |
| PMS2       | ↑             | 15%            | 15%–20%           | ↑                | ↑            | ↑               | ↑                  | ↑                | ↑        |                |                                   |                        |             |        |

(Continued on next page.)
Table 2. (Continued)

| Gene | Breast cancer | Ovarian cancer | Endometrial cancer | Colorectal cancer | Gastric cancer | Pancreas cancer | Hepatobiliary cancer | Intestinal cancer | Melanoma | Prostate cancer | Renal and urinary tract cancer | PGL/PCC and endocrine | Brain tumors | Others |
|------|--------------|----------------|--------------------|------------------|----------------|----------------|---------------------|-------------------|----------|----------------|-------------------------------|------------------|-------------|--------|
| PTEN | 25%–85%      | 5%–28%         | 9%–16%             |                  |                |                | 6%                  | 15%–34%           | 3%–38%   | 32%            | (cerebellar gangliocytoma)   |                  | 90%         | ↑      |
| RB1  | ↑            |                |                    |                  |                |                |                     |                   |          |                | (soft tissue sarcoma, osteosarcoma) |                  |             | ↑      |
| RET  |              |                |                    |                  |                |                |                     |                   |          | 50%            | (PCC); >90% (thyroid)      |                  |             | ↑      |
| SDHB |              |                |                    |                  |                |                |                     |                   |          | 77%            |                               |                  |             | ↑      |
| SDHD |              |                |                    |                  |                |                |                     |                   |          | 86%            |                               |                  |             | ↑      |
| SMAD4|              |                | 40%–50%            | 21%              |                |                |                     |                   |          |                | 15%–17% (lung); 9% (testicular tm) |                  |             | ↑      |
| STK11| 45%–50%      | 21%            | 9%–10%             | 39%              | 12%–29%        | 11%–36%        | 13%                 |                   |          |                | 15%5%/22%–11% (soft tissue sarcoma–osteosarcoma; women/men) |                  |             | ↑      |
| TPS3 | 54%          |                |                    |                  |                |                |                     |                   |          | 6% (women); 19% (men) |                               |                  |             | ↑      |
| TSC1 |              |                |                    |                  |                |                |                     |                   |          |                | 2%–5%                         |                  |             | ↑      |
| TSC2 |              |                |                    |                  |                |                |                     |                   |          |                | 2%–5%                         |                  |             | ↑      |
| VHL  | 5%–17%       |                |                    |                  |                |                |                     |                   |          |                | 25%–37% (PCC) ↑ (hemangio-blastoma) |                  |             | ↑      |
| WT1  |              |                |                    |                  |                |                |                     |                   |          |                | 74%                          |                  |             | ↑      |

Moderate/increased risk genes that are acknowledged in NCCN guidelines for initiation of early screening and risk reduction measures in accordance with family history

| ATM  | 2–4-fold | ↑ |                  |                  |                  |                  |                     |                   |          |                | (Wilms Tm) |                  |             | ↑      |
| BLM  | 2–5-fold | ↑ |                  |                  |                  |                |                     |                   |          |                | (Wilms Tm) |                  |             | ↑      |
| BRIP1| 6%        |    |                  |                  |                  |                |                     |                   |          |                |                  |                  |             | ↑      |
| CHEK2| 2–4 fold | ↑ | 2-fold           |                  |                  |                |                     |                   |          |                |                  |                  |             | ↑      |
| GALNT12 | ↑ |    |                  |                  |                  |                |                     |                   |          |                |                  |                  |             | ↑      |
| GREM1| ↑         |    |                  |                  |                  |                |                     |                   |          |                |                  |                  |             | ↑      |

Cumulative lifetime risk for any cancer: 85%–89% for women; 56% for men

(Continued on next page.)
Table 2. (Continued)

| Gene    | Breast cancer | Ovarian cancer | Endometrial cancer | Colorectal cancer | Gastric cancer | Pancreas cancer | Hepatobiliary cancer | Intestinal cancer | Melanoma | Prostate cancer | Renal and urinary tract cancer | PGL/PCC and endocrine | Brain tumors | Others |
|---------|---------------|----------------|--------------------|-------------------|----------------|-----------------|----------------------|-------------------|----------|----------------|---------------------------------|------------------------|--------------|--------|
| NBN     | 2–4 fold      |                |                    |                   |                |                 |                      |                   |          |                |                                 |                        |              |        |
| POLD1   |               | ↑              |                    |                   |                |                 |                      |                   |          |                |                                 |                        |              |        |
| POLE    |               | ↑              |                    |                   |                |                 |                      |                   |          |                |                                 |                        |              |        |
| RAD51C  | 5 fold<sup>a</sup> |               |                    |                   |                |                 |                      |                   |          |                |                                 |                        |              |        |
| RAD51D  | 6 fold<sup>a</sup> |               |                    |                   |                |                 |                      |                   |          |                |                                 |                        |              |        |

Genes that have high risk based on published studies but pending professional recommendations regarding surveillance and risk reduction strategies:

AIP<sup>33%–66% (pituitary)</sup>

ALK<sup>57% (neuroblastoma)</sup>

CDK4<sup>74%</sup>

FH<sup>10%–20%</sup>

FH<sub>a</sub><sup>98% (uterine and cutaneous leiomyoma/fibroids)</sup>

FLCN<sup>6%–41%</sup>

<sup>PGL, paraganglioma; PCC, pheochromocytoma; WT, Wilms tumor; tm, tumor.</sup>

<sup>*With positive family history; ↑: increased.</sup>
become apparent that there is a bias of ascertainment in the early literature in that re-
search studies tended to include patients with the most significant family histories.
According to one recent multigene panel study, mutations found in >40% of patients
(n=32/74) would not have been considered for testing based on personal cancer and
family history information before the introduction of panel testing strategy (Ricker et al.
2016).

With the availability of larger and larger panels, a key question has been deciding which
panel to use for which patient. Many patients who received negative BRCA1/2 results many
years ago before gene panels were available are returning to update their genetic testing to
include more genes to guide management for themselves and their families. This strategy
can exclusively be beneficial for patients, for example, with early age of onset (<50 yr of
age), bilateral breast cancer, multiple types of cancer, and/or strong family history of breast
and/or other cancers. Insurance companies have generally been covering such updates
from testing performed many years ago, often because the patient’s insurance carrier has
changed in the interim. However, insurance companies are not always covering expansion
of testing from a small panel of genes to a larger panel of genes if the former does not pro-
vide an answer if performed within a short period of time by the same carrier, and labora-
tories may not have a mechanism to bill if all the billable CPT codes were used at the
time of the original small panel testing. For that reason, some providers are ordering larger
panels initially because of concerns that subsequent testing will not be covered by
insurance.

The increased demand for genetic testing has led some insurers to require a session
with genetics professional before authorization of genetic testing (Hooker et al. 2017).
There are significant challenges to genetic education/counseling when the number of
genes tested increases from one to two genes to dozens of genes. The education/coun-
seling has, out of necessity, become much more general in terms of the clinical utility of
genetic testing rather than education/counseling about specific genes such as BRCA1/2.
Because it is impossible to educate patients about all possible manifestations in all of the
genes identified, tiered and binned genetic counseling models have been developed
(Bradbury et al. 2015).

These genetic education/counseling sessions tend not to focus on rare circumstances in
which patients are found to have mutations in genes with impact across a broad range of can-
cers and across the life span including children (TP53) or on genes associated not only with
cancer but also autism and neurocognitive and behavioral issues (PTEN) (Goffin et al. 2001;
Orrico et al. 2009).

With more expansive testing, we have begun to recognize that de novo mutations may
rarely be observed in early-onset cancers, especially in children (Oberg et al. 2016), likely
because of effects on reproductive fitness. Hereditary genetic testing was previously not rou-
tinely performed in children, but it is now recognized that ~10% of cancers in children are
due to germline mutations in some of the same genes encountered in adult cancers
(BRCA1, BRCA2, PALPB2, CHEK2, TP53, MSH2, VHL) and also in genes specific to children
such as DICER1, WT1, REST, CREBBP, ABCB11, GPC3/4 (Zhang et al. 2015; Parsons et al.
2016; Scollon et al. 2017). Rarely were biallelic mutations identified in autosomal recessively
inherited conditions. In many instances, the type of cancer and family history were not
strongly suggestive of the hereditary cancer syndrome (Parsons et al. 2016). Most of the can-
cer predispositions in children are inherited, and identification of these genes in children also
helps to identify other family members at risk (Mody et al. 2017). Panels are now available for
pediatric cancers specifically (Table 1).

In addition to the cancer implications of many of the genes on panels, some of the genes
also have reproductive implications for autosomal recessive pediatric conditions such as
ataxia telangiectasia or Bloom syndrome (Table 3).
| Gene   | Pediatric condition/inheritance (#OMIM) | Clinical features in addition to cancer predispositiona |
|--------|-----------------------------------------|--------------------------------------------------------|
| ATM    | Ataxia telangiectasia/AR (#208900)      | Progressive cerebellar ataxia beginning between ages 1 and 4 years, oculomotor apraxia, choreoathetosis, telangiectasias of the conjunctivae, immunodeficiency, frequent infections |
| BRCA2  | Fanconi anemia-D1/AR (#605724)          | Progressive bone marrow failure, short stature, abnormal skin pigmentation, skeletal malformations of the upper and lower limbs, microcephaly, and ophthalmic and genitourinary tract anomalies |
| PALB2  | Fanconi anemia-N/AR (#610832)           |                                                       |
| RAD51C | Fanconi anemia-O/AR (#613390)           |                                                       |
| BLM    | Bloom syndrome/AR (#210900)             | Severe pre- and postnatal growth deficiency, sparseness of subcutaneous fat tissue throughout infancy and early childhood, and short stature throughout postnatal life that in most affected individuals is accompanied by an erythematous and sun-sensitive skin lesion of the face. |
| BMPR1A | Hereditary hemorrhagic telangiectasia/AR (#175050) | Epistaxis, telangiectasias, (pulmonary) arteriovenous malformations, and digital clubbing |
| SMAD4  |                                        |                                                       |
| FH     | Fumarate hydratase deficiency/AR (#606812) | Severe neonatal and early infantile encephalopathy, dysmorphic features, microcephaly, cerebral atrophy, corpus callosum agenesis/hypoplasia, hydrocephaly |
| NBN    | Nijmegen breakage syndrome/AR (#251260) | Progressive microcephaly, intrauterine growth retardation and short stature, recurrent sinopulmonary infections |
| PTCH1  | Gorlin syndrome /AD (#109400)           | Macrocephaly, frontal bossing, coarse facial features, facial milia, skeletal anomalies (e.g., bifid ribs, wedge-shaped vertebrae), ectopic calcification (falx) |
| PTEN   | Cowden syndrome (#158350), Bannayan–Riley–Ruvalcaba syndrome (#153480), macrocephaly/autism syndrome (#605309)/AD | Macrocephaly, trichilemmomas, and papillomatous papules, pigmented macules of the glans penis, autism |
| TSC1/2 | Tuberous sclerosis complex/AD (#191100, #613254) | Abnormalities of the skin (hypomelanotic macules, facial angiofibromas, shagreen patches, cephalic plaques, unequal fibromas); brain (cortical dysplasias, subependymal nodules and subependymal giant cell astrocytomas [SEGAs], seizures, intellectual disability/developmental delay, psychiatric illness); kidney (angiomylipomas, cysts); heart (rhabdomyomas, arrhythmias); and lungs (lymphangioleiomyomatosis [LAM]). |

*aDisease characteristics are obtained from GeneReviews entries.*
CHALLENGES OF PANEL TESTING AND BEYOND

Although we can inexpensively generate large amounts of sequence data, our ability to accurately interpret much of this information, particularly for missense variants, is still limited, leading to a significant increase in the numbers of variants of unknown significance (VUSs) as the sizes of the panels increase (Susswein et al. 2016).

The increased frequency of VUSs with the increasing number of genes evaluated is the major disadvantage to ordering excessively large gene panels. As many as 44% of patients will receive one or more VUS depending on the primary cancer site and the test ordered (Lynce and Isaacs 2016). Although many laboratories are centrally depositing data in ClinVar to facilitate data sharing and resolution of uncertain results, not all laboratories performing cancer genetic testing are depositing their data. Insurance companies have in some cases applied pressure to improve data sharing and will only reimburse for testing performed at laboratories that deposit data in ClinVar. With increasing availability of large amounts of sequence from population-based cohorts of increased ethnic diversity (ExAC and gnomAD) and with high-throughput functional assays (Millot et al. 2012; Guidugli et al. 2014; Gasperini et al. 2016), it should be possible to interpret an increasing number of VUSs, and it will be critical for such reinterpreted data to be returned to clinicians and patients as it is available to guide management. Updated interpretations will be particularly important for minority patients who have a disproportionately higher frequency of VUSs (Minion et al. 2015; Ricker et al. 2016; Susswein et al. 2016) and a lower genomic literacy to understand the nuances of a VUS (Lumish et al. 2017).

VUSs are particularly challenging for hereditary cancer predisposition syndromes because there is no independent clinical method to evaluate the pathogenicity of a variant. VUS results were found to escalate the intention to increase cancer screening practices in patients with personal cancer history or only positive family history even though patients should be counseled to follow personal and/or family history–based guidelines in the absence of an identified mutation (Lumish et al. 2017).

The major benefit of screening individuals for hereditary cancer predisposition comes from effective medical/surgical management and preventive measures (Kurian et al. 2010). We still do not have clinical surveillance and management guidelines for many of the relatively new, moderate- or low-penetrance risk genes (Table 2). For moderately penetrant genes such as ATM, which is associated with a twofold increased risk of breast cancer (Thompson et al. 2005; Renwick et al. 2006), surveillance and management recommendations will often not change if there is a personal or family history of breast cancer. For classically highly penetrant genes such as CDH1 and TP53, it is unclear if the penetrance for mutation carriers who do not have a personal or family history of cancer is similar.

To address the questions of penetrance, cancer spectrum, and recommended clinical management, we need more data to enable better genotype–phenotype correlations, to estimate age- and gender-specific penetrance and expressivity, and to identify modifiable risk factors through increased data sharing. Some public registries such as ENIGMA (https://enigmaconsortium.org) and PROMPT (http://promptstudy.org) support these studies, but the amount of data in these registries is a small fraction of the number of mutation carriers being identified clinically. It would be much more efficient and effective if patients were given the option of contributing de-identified clinical data to researchers to generate knowledge-based recommendations that will one day directly benefit the care for themselves and their families.

Some genes such as APC, VHL, and TP53 have relatively high de novo mutation rates (Hes et al. 2008; Prochazkova et al. 2009; Wu et al. 2012, 2013), and family history is not contributory in those cases and makes these diagnoses more unexpected for the patient and
clinician. Additionally, TP53 mutations are not uncommonly detected as somatic mutations in blood and may be incidental but must be differentiated from germline mutations by performing a skin biopsy (Pospisilova et al. 2012; Slavin et al. 2015).

Analysis of some genes such as PMS2 is particularly complicated because of highly homologous pseudogenes (van der Klift et al. 2016). These regions are difficult to uniquely map with short-read NGS-based panels; therefore, some clinically significant variants in those regions may not be easily detected, and sensitivity for mutations in these genes can differ by the methods beyond the short-read NGS used by the laboratory to interrogate these regions.

In recent years, matched tumor-germline and tumor-only sequencing studies identify actionable germline mutations that can guide the therapeutic management of the cancer (e.g., BRCA1/BRCA2 mutations and Olaparib) (Hennessy et al. 2010; Ledermann et al. 2014; Kurian et al. 2017) and prevention of future associated cancer. With tumor sequencing, 5%–15% of patients unselected for family history are found to harbor pathogenic or likely pathogenic variants in hereditary cancer predisposition genes (Schrader et al. 2016; Seifert et al. 2016). Although this type of testing is beneficial, many patients are not receiving any genetic education or genetic counseling and may be surprised when germline results are returned. As more tumor sequence is publicly available in the Catalogue of Somatic Mutations in Cancer (COSMIC; http://cancer.sanger.ac.uk/cosmic), The Cancer Genome Atlas (TCGA; https://cancergenome.nih.gov/), and the International Cancer Genome Consortium (http://icgc.org/), annotations of germline variants will be helpful with variant interpretation.

With the increased demand for cancer panel gene testing, there is an increased need for genetic education and genetic counseling and an inadequate number of genetic professionals to provide these services. There is a need to train additional genetic counselors, to train other providers to provide care in genomic medicine, and to develop education tools including easily understandable and culturally appropriate educational videos to enable the provision of appropriate care to patients on scale.

**DETERMINANTS OF TEST SELECTION**

Choosing the right panel depends on multiple factors (Fig. 1). Family history is important, but can be limited by small family size or gender distribution, early deaths due to nonmedical causes, or lack of information about family members’ medical issues. The high population prevalence of cancer in older individuals may also obscure the pattern of cancers attributable to genetic factors versus other environmental causes and make selection of the right panel more difficult.

Cost and coverage for testing are important factors. BRCA1/2 is the one genetic test covered under the Affordable Care Act. Many insurance companies, Medicaid, and Medicare have guidelines for genetic testing for common cancers. The cost of testing has come down as low as $250, enabling some patients to pay out-of-pocket for testing even when not covered by insurance.

Laboratories differ slightly in their gene composition, techniques for detecting insertions/deletions/rearrangements, variant interpretation approaches, variant reinterpretation policies, reference database, and what they include in their test reports and how they present the information. Most of the high-volume cancer genetic laboratories offer options for panels of various sizes and composition to tailor to the needs of patients by cancer type. Some laboratories also offer a la carte options to select specific genes of interest for the patient.

As the cost of sequencing continues to drop, WES has been considered as an alternative to panels. Targeted gene panels have some advantages over WES in terms of average mean
read depth and coverage of genes of interest (Feliubadaló et al. 2017). Turnaround time is shorter with targeted gene panels because the amount of data to analyze is considerably less. WES can be considered for patients with multiple primaries at young ages, and/or a strong family history of site-specific cancer with normal genetic test results from a large panel on at least one affected individual. There are certainly likely to be novel hereditary cancer genes to be discovered; however, given the large size of largest panels, results from WES are likely to identify novel genes that will necessarily be of uncertain significance until more data is gathered on these genes. Increasingly, genomic sequencing data will be available on paired tumor/normal tissue samples that may help to identify some of these novel genes.

WHAT WILL THE FUTURE HOLD?

Given the relatively widespread adoption of panel gene testing to date and the clear value in making molecular diagnoses that otherwise would have been missed by routine clinical guidelines, we suggest that panel gene testing will continue to be the norm in hereditary cancer testing. As data are available to better interpret variants, as systems are put in place to deal with reinterpretation of VUSs, and as providers become educated about how to manage patients with VUSs, the concern about receipt of VUSs will be less of a deterrent to large panels. The field will likely shift to offering germline genetic testing to all patients with breast, ovarian, uterine, colon, stomach, pancreas, prostate, and renal cancers, pheochromocytomas, and sarcomas for a panel of genes associated with high risk and with NCCN guidelines for these cancers. Germline testing will increasingly be done in parallel with tumor testing for a panel of genes/mutations that are actionable for treatment. Beyond this “basic panel” of high-risk genes with NCCN guideline, expanded panels including newer genes of uncertain penetrance and moderate/low risk genes will be incorporated with polygenic risk scores derived from approximately 100 common polymorphisms to provide more accurate and comprehensive risk stratification. An alternative option will be exome/genome sequencing as the cost of sequencing comes down with the new NovaSeq sequencers and as interpretation systems are developed to efficiently analyze thousands of variants simultaneously.
Population-based screening of unaffected individuals is also likely to gain traction with the introduction of less expensive cancer panel testing, especially if it can be proven to be cost-effective in the general population (Gabai-Kapara et al. 2014; Long and Ganz 2015).

As we move forward with advances in genomic medicine, we are building the plane as we are flying it. To enable advances to be made as quickly as possible for the patients who can benefit from genomic advances, we need to embrace sharing and distribution of de-identified clinical and genetic data collected in the process of routine clinical care, strongly protect the privacy of patients’ data, and commit to returning the new knowledge we acquire to patients who need and deserve the information.

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