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The Future of Clinical Cancer Genomics

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Whether or not it was first said by atom-splitter Niels Bohr or splitter-ball catcher Yogi Berra, we all agree “it’s tough to make predictions- especially about the future.” In the concluding section of this monograph on the current status of predictive cancer genomics, it is appropriate to ponder the future of this translational field of medical science. As will also be addressed here, it is particularly instructive for the providers and consumers of the rapid advances in genomics and medicine to make their own predictions of the impact of “personalized genomics” on preventive oncology.

This effort to encourage introspection is meant to highlight the sea change that is shaping the way genomic predictive markers have been integrated in the practice of “precision medicine.” The elements of this sea change are multifold and have constituted a virtual “perfect storm” which is now raining down on the clinical practice of cancer genomics. As will be discussed here, these factors include: the rapid advances in genomic science and technology that allow massively parallel sequencing of both tumors and the germline^{1,2} a landmark shift in interpretation of statutes bearing on intellectual property of genetic discoveries³, rapid expansion of access to the internet, including mobile access to both genomic data and tools to interpret these data in a medical context, the expansion of for-profit genomic diagnostics – some masquerading as “recreational genomics,” and a worrisome view of medical professionals as barriers to rather than facilitators of understanding one’s genome. Each of these factors will impact how the discipline of predictive and preventive oncology is able to shape the translation of genomic technologies in the most responsive and responsible way. Here, we shall lay out the challenges and potential conflicts in bringing “personalized genomics” to oncology. I will use as a framework a prior essay on this topic⁴, updating and expanding these observations based on recent developments in the clinic, in clinical and translational laboratory research, in the courts, and in the economic and social infrastructure that impact how cancer patients and these at risk for cancer are offered genomic information.

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Shifting Paradigms in Cancer Genomics: 1. Causative Events, Consequences, and Emerging Strategies

In his classic monograph *The Structure of Scientific Revolutions*⁵, the historian of science Thomas Kuhn coined the term “paradigm shift” to characterize periods of sudden departure from “normal science” when “unprecedented” discoveries shift the very practice of science in a fundamental, revolutionary way. To a real extent the rapid pace of the “genetic revolution” has impacted medicine. Perhaps in no other area has this change been more dramatically felt than clinical cancer genomics.

The preceding chapters of this monograph have updated our current knowledge of inherited mechanisms of cancer susceptibility. They have presented new information about genotype and phenotype, risk prediction, and targeted intervention. However, this monograph can only give hints at what lay ahead, since the major forces which will drive changes in clinical genomics are only now coming into maturity. Thomas Kuhn stated that to meet the bar of a paradigm shift, the new advances must be “sufficiently unprecedented to attract an enduring group of adherents away from competing modes of scientific activity.” He predicted that a true paradigm shift would be “sufficiently open-ended to leave all sorts of problems for the redefined group of practitioners to resolve.” Here, we will argue that the factors driving the paradigm shift in cancer genomics are not only on the verge of changing the medical model for delivering cancer genetic information but of replacing it entirely.

Consequences of Current Generation DNA Sequencing

Compared to Sanger capillary-based sequencing, massively parallel sequencing, touted as “Next Generation Sequencing” (NGS), is now part of current generation practice. NGS employs simultaneous sequencing reactions detected automatically, producing millions of sequence calls per instrument run, at a significantly lower expense. Recent advances have increased the number of nucleotides per sequence read (or read lengths) and lower cost and greater base-calling accuracy¹. These technologies have been applied to sequencing of exomes, entire genomes, and exons and splice region sequences of selected genes. The research impact of NGS technologies on the pace of new syndrome identification has been remarkable. By sequencing relatively few members of families with recurrent and unexplained malignancies it has been possible over just the past few years to identify over a dozen new cancer syndromes (Table 1). Only some of these new syndromes have been included in the preceding sections of this monograph, as these discoveries are so recent that precise genotype-phenotype correlations have yet to be established. As an example of the challenges of clinical translation posed by these NGS discoveries, we described two new syndromes of predisposition to childhood acute lymphoblastic leukemia^{6,7}, both caused by inherited mutations of transcription factors. While there was compelling functional biological evidence of “causation” behind the association of these germline mutations and the familial occurrences of leukemia, both syndromes demonstrated incomplete penetrance, and for both there was no proven preventive intervention other than pre-implantation genetics to halt transmission of the trait. Such reduced penetrance is the rule rather than exception for most if the NGS syndromic discoveries listed in Table 1.

In addition to their role powering whole genome discovery, NGS technologies have also impacted the rapid diagnosis of known syndromes by utilizing “capture” of exons and exon-intron splice regions of dozens of cancer predisposition genes, all analyzed simultaneously, as part of a new breed of multiplexed diagnostic panels⁸. As will be discussed, this technological innovation has stimulated the appetite of both providers as well as consumers of genetic tests, in favor of “prix fixe” menus of multiple gene tests at costs lower than that of the old “a la carte” menu of phenotype-directed genetic analysis.

Fallout of the End of Gene Patenting

Just as NGS technologies began to generate novel syndromic discoveries of potential diagnostic value, the U.S. Supreme Court ruled that isolated genomic DNA was not patent-eligible under section 101 of the Patent Act. The court, however, let stand patents for cDNA, an approach which some of us predicted before the decision, and which was to have an impact on the practice of preventive oncology³. The opinion written by Justice Thomas was unanimous and brief. The oral argument, at least to this listener, was notable for the absence of understanding both by the Justices and the U.S. Solicitor General of basic concepts of genetics (e.g. the difference between DNA and RNA), and the use of non-scientific metaphors, involving trees, baseball bats, etc. The late Justice Scalia wrote that he agreed with the majority opinion even though he admitted he did not feel educated enough on the topic to sign the recitation of “the details of molecular biology.” Within a few days of the decision, as *N.Y. Times* reporter Andrew Pollack sought confirmation from many of us that it would be a very short time before academic and for-profit genetic testing companies would make available NGS for panels including *BRCA1/2*⁹, many also expressed concern that broad deployment of these multigene panels was premature in the absence of regulatory oversight of quality of testing, evidence of clinical utility, and strategies to interpret genetic variation⁸.

Awash in Variants of Familiar and Novel Genes

Despite the warnings, the rush to multigene panels left clinicians coping with interpretations of reports of variants of unknown significance (VUS), with such findings as frequent as 10–90% depending on gene and panel¹⁰. Of more concern, anecdotal experience revealed some ill-informed health practitioners recommending preventive surgeries following VUS detection. And even more challenging, the multiplex panels included genes for which mutations were only known to be associated with low to intermediate penetrance, and genes for which mutations had unclear clinical utility and were previously not recommended for clinical testing. For example *CHEK2*, recommended as of unclear clinical utility in the era of single gene testing,¹¹ was now routinely included in multigene panels. Valiant efforts were made to catalogue current knowledge of disease specific gene of varying penetrance.¹² As new genes came to be discovered by NGS strategies (represented in Table 1), they often were added to existing panels, even in the absence of data on associated phenotypes and penetrance.

Initial Response of Federal Agencies and the Academy to the Genomic Tsunami

Just as the “tsunami” from the perfect storm of NGS breakthroughs, internet marketing, and the lifting of IP restrictions hit clinical oncology, one federally supported body charged with

interpreting the evidence basis for genomic diagnostics, including those for cancer susceptibility, experienced a 95% budget reduction. This group, called The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Initiative, funded largely by the CDC, had produced a number of evidence reviews bearing on cancer^{13–16}. But EGAPP was not to be fully available for the sudden commercial proliferation of multigene panels in cancer risk testing. To address the most pressing need for cross-sectional databases, to document genetic variation and curation, and in the absence of a unified strategy from the for-profit laboratories to address the consequences of premature deployment of multigene panels, spontaneous initiatives were launched by other stakeholders. The *BRCA* Global Challenge was organized by a combination of governmental, commercial, and academic groups to seek to establish a universal database of *BRCA* variants¹⁷. The NHGRI organized investigators through ClinGen¹⁸ to form a Cancer Working Group to establish databases and strategies to curate key cancer susceptibility genes such as *PTEN*, and deposit these data into ClinVar¹⁹. At the same time, we at Memorial Sloan Kettering Cancer Center, and colleagues at the University of Pennsylvania, the Mayo Clinic and the Dana Farber Cancer Institute, built an on-line portal open to all individuals who had multigene panel testing. This initiative, called the Prospective Registry for Multiplex Testing (PROMPT) aimed to create a cohort for study of penetrance and outcome, and has over two thousand participants and is growing. The effort was joined by the seven largest commercial laboratories, who added onto their reports the link for patients with VUS and/or mutations in intermediate penetrance genes to consider joining this registry²⁰. Indeed, all oncologists, genetic counselors, and others ordering multigene panel tests are encouraged here to provide their patients with links to join the PROMPT registry (www.promptstudy.org) An immediate observation of the PROMPT registry, presented as a 2016 ASCO abstract, was a substantial rate of divergent reports among the commercial laboratories. Such a finding is consistent with reports at recent meetings of the Clinical Sequencing Exploratory Research groups of the NHGRI documenting divergent results of “bake off” exercises of carefully blinded variant curation comparisons among experts²¹. These findings underscore the risks of the premature deployment of these technologies.

Response from Payers

Some third party payers had already recognized that the increasing cost of cancer diagnostic testing could be manipulated by decreasing access. Based on perceptions of the need for continued physician education in the realm of cancer genetic testing and the effectiveness of genetic counseling, one insurance carrier put in place policies to deter licensed oncologists from ordering *BRCA* tests. In the name of “quality improvement,” such tests were approved only if patients were first screened by genetic counselors who were either funded by the insurer, or accessed via directed consultation to determine if a test was indicated^{22,23}. This strategy established a *de facto* filter to access to cancer genetic testing²⁴ and also raised a potential challenge of restraint of the practice of cancer medicine by oncologists seeking to order genetic tests to guide therapy (e.g. PARP inhibitors) as well as prevention.²³ With the planned expansion of these policies, a prediction for the future is a confrontation between practitioners and at least one large payer over the issue of scope of practice.

Less May Be More In Germline Genomic Scans

The advent of multigene testing served to galvanize some payers to seek to limit their use, on the basis of the unproven clinical utility of all gene tests included on the panels²⁵. Within the “expert committees” such as the National Comprehensive Cancer Network, NCCN, there has been healthy and ongoing debate and efforts to ensure that guidelines, monitored closely by insurers, reflect the rapidly changing evidence base. At present and going forward, there will be a trend to reimburse only those tests for which there is proven clinical utility, with clinicians and patients facing a web of different thresholds for testing varying by laboratory or type of third party provider.

There is also an emerging “push back” among both patients and providers against the obligate “*prix fixe*” model of multiplex testing. It was a hallmark observation of clinical genetics that from a third to a half of patients counseled for suspected Li Fraumeni syndrome would defer p53 testing. *TP53* testing, if offered as an option, was not desired for inclusion on the test panel by a proportion of patients offered multi-gene testing (Robson M, personal communication). Many clinicians would also like to be able to exclude or include specific genes depending on phenotype, and lack of clinical utility for some genes on “panels.” (e.g. *CDHI* in non-lobular breast cancer). Thus, another prediction for the future is the movement toward physician and provider selected panel compositions.

Going forward, increasing numbers of labs are offering “custom” gene panels, in most cases running the larger panels internally, but “filtering” reported results only to what is requested. This strategy allows both consumers and genetics professionals to request only those tests which have evidence of clinical utility, or which are based on phenotype. Clinicians (and their patients) can then defer other results until data on clinical utility emerges, thus reserving for the laboratories the future option to report additional results - and perhaps recover costs. Such a strategy of maintaining identified potentially actionable genomic data will likely require documented prospective consent. Unlike the “diagnostic odyssey” which often justifies whole exome testing in the evaluation of some dysmorphic children, and will be documented by NHGRI funded studies in progress, the burden of “duty to warn” of non-cancer predispositions raises significant challenges for adults subjected to whole exome germline tumor-normal screens^{26,27}

Shifting Paradigms In Cancer Genomics: 2. The Tale of Two Genomes, Screening, and Pharmacogenomics

Just as NGS technology allowed multiplex gene-panel testing, the second wave of the NGS tsunami impacted the clinical application of genome-wide re-sequencing of tumors to guide targeted therapies. In the process, the patients’ “normal” or inherited DNA is typically also scanned, raising immediate medical as well as ethical challenges.^{26,27} While one commercial laboratory and many academic laboratories purposely avoid sequencing normal DNA as a comparator for the tumor DNA, it is now clear that inclusion of such reference normal sequence adds to the sensitivity of the assay²⁸. Initial tumor sequencing strategies have simply “subtracted” inherited variation from the tumor genomic reports, resolving some of the ethical and medical complexity surrounding consent for familial cancer risk

testing at time of diagnosis of malignancy.²⁶ Anonymized retrospective analyses of tumor-normal genomic data from several large centers^{28–32}, published at the outset of 2016 (Table 2) demonstrated that within the germline compartment of tumor-normal sequence data, is a trove of clinically relevant information. While many of these early reports have focused on common adult and pediatric cancers, a number of other studies will appear in 2016 and 2017. In our early series of adult cancer cases, inherited mutations of cancer susceptibility genes which were clinically “actionable” were noted in about 10 % of cases. Importantly, these studies and others to be published later in 2016, will identify significant proportions of cases of breast, ovarian, prostate, and other cancers with inherited mutations of DNA homologous repair genes, potentially amenable to therapy with PARP inhibitors, as well as subsets with Lynch associated mutations, potentially amenable to immunotherapy. In the MSK series, and others, there were also a fascinating set of cases where germline mutations in known genes (e.g. *BRCA1/2*, *RET*) occurred in tumors not part of known syndromes.

These findings have led our institution to collect tumor-normal DNA sequence in the setting of a consent process which explains that if inherited markers of cancer susceptibility are found, and if the patient desires, these results will be communicated in the context of genetic counseling. This so called “opt in” approach may soon be replaced by an “opt out” approach, where communication of germline findings is the “default” setting, unless the patient does not wish to know this information. Pending these refinements, a tiered approach to informed consent for NGS studies (Figure 1) will provide germline cancer risk assessment at the same time as tumor mutations are assessed as therapeutic targets. Thus, one of the evident future scenarios for clinical cancer genomics is a “tale of two genomes” where both tumor and inherited information is made available to all cancer patients at the time of diagnosis, with the “cascade” of genomic information to unaffected relatives for use in targeted prevention and even reproductive planning.

Population Screening

It was evident even at close of the first wave of cancer predisposition gene discovery in the 1990’s that genetic testing could lead to early diagnosis and prevention of many breast, ovarian, colon, thyroid, stomach, and pediatric cancers³³. For breast and ovarian cancer evidence supported decreased mortality due to breast and ovarian cancer.³⁴ However, current guidelines limit *BRCA* testing to those with strong family histories of breast or ovarian cancer and/or early age of onset of disease, “triple negative” breast cancer affected before age 60, those with invasive ovarian cancer, and individuals of Ashkenazi origin with breast cancer.³⁵ The U.S. Preventive Services Task Force has not endorsed population based *BRCA* screening.^{36,37} Nonetheless, with the advent of NGS technologies, during the past year some have come to call for population based *BRCA* testing.^{38,39} A thoughtful discussion concluded that population-based *BRCA* screening would likely accentuate health access and resource limitations, particularly for minority women, and could result in false-negative results in the absence of professional genetic counseling, false positives due to incorrect interpretation of variants of uncertain significance, as well as other potential harms due to psychosocial factors⁴⁰. However, a different argument can be made for genetic screening in “founder” populations such as is the Ashkenazi Jews, where we described a single *BRCA2* mutation present in over 1%, and 1 in 40 individuals carrying one of three *BRCA1/2*

mutations.^{41–44} Strikingly, 26–55% of individuals with *BRCA* mutations will be missed if testing is limited to criteria based on family history,^{45–51} and some of these cases invariably will represent potential lives lost if *BRCA*-based surgical or medical interventions are not initiated.⁵² Indeed *BRCA* population based screening in Ashkenazi Jews (AJ) has been performed in pilot studies^{53,54} and is cost effective; the cost per cancer detected was nearly 40 fold less expensive in Ashkenazi Jews compared to non Ashkenazim.⁵⁵ A group of us are committed to initiating a population based study to offer *BRCA* testing to Ashkenazi Jews in the context of a “medical model” that provides appropriate counseling.⁵⁶ The results of this trial may offer important guidance into the integration of genomics into mainstream medical practice. Other large scale studies are underway to provide genomic sequencing in 100,000 individuals⁵⁷ as well as other studies as part of federal as well as academic “precision medicine” initiatives.

The Belated Arrival of Pharmacogenomics

Pharmacogenomics assesses inherited (or acquired) genetic abnormalities to predict treatment response or outcome. Despite anticipation a decade ago of its explosive impact on the field of oncology, the clinical utility established by pharmacogenetic studies in cancer have been limited to a handful of variants linked to treatment response (e.g. *UGT1A1*, *CYP2D6*) and a plethora of genome-wide studies of response and toxicity⁵⁸, including some with a high level of interest in clinical application⁵⁹. Recently rare variants have been associated with cardiotoxicity following anthracycline based chemotherapy, an issue of pressing clinical relevance for those planning adjuvant and/or curative treatments of a number of hematopoietic and solid tumors. One such finding was that a coding variant in *RARG* appeared to be associated with cardiotoxicity following childhood cancer.⁶⁰ A major challenge of pharmacogenomic studies remains the need for large numbers of well-phenotyped patients treated with the same dosage and type of chemotherapy. Successful pharmacogenomic studies conducted in *in vitro* cell-based models, with confirmation of findings *in vivo*, now provide an important approach to move this field forward, with initial GWAS data providing identification of SNPs predicting, for example, response to platinum in patients with urothelial (or other) carcinoma, and in colorectal and prostate cancer.⁵⁸ One would clearly anticipate that an inevitable result of the era of expanded tumor-normal sequencing, will be the identification of variants associated with treatment out come and toxicity.

Shifting Paradigms in Cancer Genomics: 3. Concluding Comments on the “Demedicalizing” of Cancer Genomic Testing

As mentioned at the outset, a “perfect storm” of factors, including scientific discovery of new cancer susceptibility genes, the availability of large scale genomic sequence data unfettered by intellectual property limitations, mobile access to the internet, entrepreneurial investment in for-profit genomics, and exhortations to end “genetic exceptionalism” by non-clinician enthusiasts of direct to consumer genetic testing, have led to a view of medical professionals as barriers to rather than facilitators of understanding one’s genome. Each of these factors will impact predictive and preventive oncology.

To illustrate the scope of these challenges to predictive oncology, Table 3 lists potential future scenarios for clinical cancer genomics. Underlying the future path chosen will be a need to understand the conflation of terminology which seeks to cast health professionals as barriers to rather than trusted guides to accessing the personal genome. On one hand, there is clear trend in biomedical disciplines for greater empowerment and participation of the patient in all aspects of research and care.⁶¹ Medical records will increasingly reflect genomic data.⁶² At the same time, while some have cast doubt on the speed of the impact of “precision oncology”⁶³, and characterized this set of changes as part of the continuum of positive but “disruptive” technologic innovation⁶⁴, most would predict that in person, phenotype-driven genetic testing will soon be replaced. Instead of extended genetic counseling sessions, there will be “automated” pretest introduction to panels of genes, with results provided by “alternative” strategies to decrease reliance on in-person communication. However, it is unclear as to the tempo of this transition. Will this paradigm shift be complete by 2020? Or 2040? Why does this matter?

Certainly the tempo of this shift to “high throughput genetic counseling and testing” matters economically for those for-profit entrepreneurs who have invested. Already some genetic testing companies have failed, while other large corporations, particularly search engines and information technology firms, have committed substantial sums toward on-line delivery of “personalized genomics.” Other than its economic fallout, the tempo of this transition to more direct, unfiltered access to individual genomic sequence matters for society. Indeed, the public health may be as much at risk from the premature deployment of de-medicalized, commercialized testing for genetic predisposition, as it is from the health threats of the syndromes of cancer predisposition themselves. According to this view, while claiming to “empower” individuals to seize rightful control of their personal genomes, for-profit companies, abetted by some fervent but clinically naïve basic scientists, are “commoditizing” the genome. By implying that healthcare professionals are now coming between the individual and the right to “know” their personalized genome, commercial companies and their distinguished (and sometime co-invested) consultants, are *de facto* seeking to exclude the one group with an explicit fiduciary responsibility to the patient, family, and individual. When independent health care providers- physicians, genetic counselors, and other health care providers- are removed from the individual’s quest for self genetic knowledge, there may be no one else to turn to except an employee of the testing organization itself, incentivized to profit from increased utilization of its services.

In de-medicalizing genomic direct to consumer testing, there was an initial appeal to the broader concept of “recreational genomics.”⁶⁵ However recreational cancer genetic testing may be more similar to recreational drug use than commercial purveyors would advertise. The important distinctions lay in the medical implications of the test, and not simply the access to the test; *TP53* germline testing for the risk of lethal- and mostly unpreventable-malignancies is quite different from testing for a predisposition to ear wax formation.

The “de-medicalizing” of cancer genetic testing is not a requirement for its increased uptake⁶⁶. There is no question that cancer predisposition testing will be more accessible in the future; it remains to be determined how fast and to what extent it should be de-medicalized. As has been shown, interpretation of variants, indications for preventive

surgeries, discussions of reproductive options, to name a few, are aspects of this discipline not casually considered. The issue is whether the “inevitable” future of cancer genomics will be thrust upon us by commercial interests, or whether that future course can be modulated in a responsible way that protects the public health while implementing powerful new medical tools for cancer prevention and early detection.

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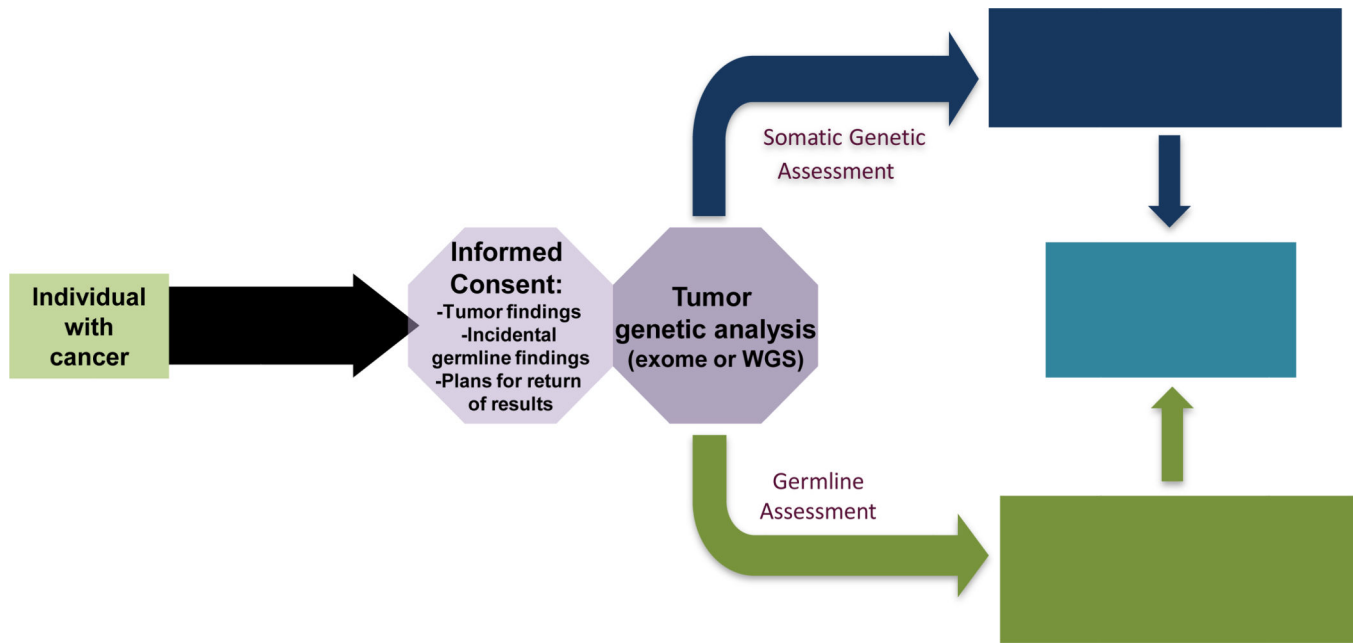


Figure 1. Next-Generation Sequencing of Tumors with Incorporation of Incidental Germline Findings (adapted from Stadler, 2014)

Table 1

Impact of Next Generation Sequencing In Discovery Of Novel Cancer Predisposition Syndromes

Familial Cancer Syndrome		NGS	Gene	Cases used to identify
Pancreatic cancer	Jones et al., <i>Science</i> 2009 ⁶⁷	Exome	<i>PALB2</i>	1 affected familial pancreatic cancer
	Roberts et al., <i>Can Disc</i> 2012 ⁶⁸	WGS	<i>ATM</i>	WGS/Exome:16/22 affecteds 6/10 families
Pheochromocytoma	Comino-Mendez et al., <i>Nat Gen</i> 2011 ⁶⁹	Exome	<i>MAX</i>	3 affecteds from 3 families
Wilms Tumor	Mahamdallie et al., <i>Nat Genet</i> 2015 ⁷⁰	Exome	<i>REST</i>	4 families
AML/MDS	Ostergaard et al., <i>Nat Gen</i> 2011 ⁷¹	Exome	<i>GATA2</i>	3 unrelated affecteds (2 w/ familial)
Familial Myeloid	Saliba et al., <i>Nat Genet</i> 2015 ⁷²	Exome	<i>ATG2B</i> <i>GSKIP</i>	4 related kindreds
Familial Melanoma	Yokoyama et al., <i>Nature</i> 2011 ⁷³	WGS	<i>TIFT</i>	1 affected with familial melanoma
	Horn et al., <i>Science</i> 2013 ⁷⁴	Tar Seq	<i>TERT</i>	4 affecteds/1 unaffected in 1 kindred
Mesothelioma/uveal melanoma/renal	Testa et al., <i>Nat Gen</i> 2011 ⁷⁵ Farley et al., <i>Mol Ca Res</i> 2013 ⁷⁶	Exome	<i>BAP1</i>	2 Kindreds 1/83 kindreds
Colorectal adenomas/ca	Palles et al., <i>Nat Genet</i> 2013 ⁷⁷	WGS	<i>POLE, POLD1</i>	20 affecteds /15 families
	Weren et al., <i>Nat Genet</i> 2015 ⁷⁸	Exome	<i>NTHL1</i>	51 affecteds/48 families
Non Medullary Thyroid	Gara et al., <i>NEJM</i> 2015 ⁷⁹	Exome	<i>HABP2</i>	7 affected 1 kindred
Breast Cancer	Park et al., <i>AJHG</i> 2012 ⁸⁰	Exome	<i>XRCC2</i>	5 affecteds from 2 families
	Park et al., <i>BCRT</i> 2011 ⁸¹	Exome	<i>FAN1</i>	4 early-onset multiple-case families
	Ruark et al., <i>Nature</i> 2013 ⁸²	TarSeq	<i>PPMD1</i>	1,150 with breast cancer +/- ovarian
	Cybulski et al., <i>Nature Genet</i> 2015 ⁸³	Exome	<i>RECQL</i>	7 cases Quebec, 30 in Poland
Ovarian cancer	Rafnar et al., <i>Nat Genet</i> 2011 ⁸⁴	WGS	<i>BRIP1</i>	457 Icelanders
ALL	Shah et al., <i>Nat Genet</i> 2013 ⁶	Exome	<i>PAX5</i>	2 kindreds
	Noetzli <i>Nat Genet</i> ⁸⁵ , Zhang <i>Nat Genet</i> ⁸⁶ , Topka <i>PLoS Genet</i> 2015 ⁷	Exome	<i>ETV6</i>	Multiple kindreds

Recent Tumor-Normal Sequencing Studies, Including Germline Findings That Are Actionable²⁸⁻³²

Table 2

Institutional Series (references 28-32)	Johns Hopkins University	University of Michigan	Memorial Sloan Kettering	St. Jude Children's Research Hospital	Baylor College of Medicine
Number Sequenced	815	91	1566	1120	150
Number of Germline Actionable Findings (N)	27	9	198	95	13
Germline Actionable Findings (%)	3%	10%	12.6%	8.5%	8.6%

Table 3

2020 Foresight: Future Paradigms for Clinical Cancer Genomics

If you would be willing to anonymously reply to this opinion survey online, please go to <https://www.surveymonkey.com/r/6XHXS5J>. Results may be posted in the future.

In your opinion, which response best characterizes the future state of predictive cancer genomics:

1	In 2020, most germline cancer genetic testing will be delivered
	<ul style="list-style-type: none"> a. By cancer genetic health care professionals using traditional forms of genetic counseling b. By a variety of health care professionals ordering tests on-line, with blood or saliva samples sent and results received online or in person, and reimbursed by carriers. c. By individuals via direct-to-consumer testing, largely self-paid, with results discussed with a health care provider only if initiated by the consumer d. In the context of treatment selection, limited by third party payers, and with results delivered as any other medical test.
2	By 2020, the assessment of the patient newly diagnosed with cancer, for largest number of cases, will include
	<ul style="list-style-type: none"> a. Tumor only testing for mutations that are shown to target therapies b. Tumor-normal testing including germline risk assessment at the same time c. Tumor-normal exome/genome/transcriptome testing with reporting of all inherited findings, including non cancer risks
3	By 2020, pre-implantation genetic diagnosis for cancer predisposition
	<ul style="list-style-type: none"> a. Will be used at about the same frequency as today b. Will be used much more often and reimbursed by carriers c. Will begin to be impacted by direct germline “editing,” prohibited in the U.S, but obtained abroad. d. Will be routinely included as part of “fitness” screens offered to all reproductive age couples, with defined indications for reimbursement by carriers
4	By 2020, pharmaco-genomic testing for cancer drug and dose selection
	<ul style="list-style-type: none"> a. Will be utilized uncommonly as drug choices and dosing will be based on other factors b. Will be routinely performed as part of pretreatment assessment of the cancer patient c. Will be performed commonly but after initiation of treatment in the assessment of severe toxicity in selected cancer patients