Integrating Personalized Medicine into Preventive Care through Risk Stratification

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RISK STRATIFICATION is a well-known concept to clinicians and is routinely practiced in clinical care. Novel means to risk assess our healthy patient population, however, are constantly evolving, especially with the growth of our ability to process and analyze big data and the subsequent development and customization of risk stratification tools. These advancements are also making steps towards medicine becoming ever more precise and personal – where we once might have stratified an adult's risk solely on his or her age and family history of disease, we are now able to improve that stratification with multiomic-approaches. By refining markers of risk for a disease, we can improve characterization of risk that leads to improved surveillance and access to preventive medications in pre-symptomatic populations before disease onset.

Phenogen's geneType Risk Prediction Suite

Phenogen's geneType is a suite of risk assessment tools that integrate common genomic markers of risk with traditional epidemiological risk factors, resulting in a net improvement in stratification over traditional risk assessments. Testing is carried out within Genetic Technologies' in-house CLIA-certified and NATA-accredited laboratory (part of the Phenogen Sciences Laboratory). Genotyping is platform-agnostic; our assays are currently carried out on a custom Illumina Infinium array and the proprietary algorithms are implemented using our custom-built analysis platform created in partnership with DNA Nexus. A polygenic risk score (PRS) is one of many critical components within our risk models, but the clinical value of PRSs is not yet widely acknowledged, in part due to a lack of consensus in PRS reporting standards.[1] We and others[2] have methodically

created a clinically validated laboratory pipeline for the implementation of genomic-integrated risk assessments. The flagship geneType product is our breast cancer risk assessment model; the clinical team has developed a number of other disease risk models built on the same foundation: polygenic plus clinical risk.

Major risk assessment categories

There are three major categories of risk assessment based on the clinical guidance available for the disease of interest:

- First, in disease areas such as breast cancer and cardiovascular disease, there are clinically recognized absolute risk thresholds for which guideline-driven clinical care can be directly applied. In these circumstances, the geneType model can be directly compared to gold standard models to show improved efficacy in prospective cohort and nested case-control analysis.[3-6]
- Second, in other disease areas such as prostate or colorectal cancer, there may not be implicit risk thresholds, but there are clinical screening guidelines based on age and family history from which we can infer levels of risk.
- Third, disease areas such as ovarian and pancreatic cancer have limited screening options available, but because we are able to stratify risk, we may be able to establish efficacious and cost-effective screening or risk-reduction methods for at-risk groups rather than the general population.

Herein, we will focus on geneType for breast cancer and its potential efficacy if implemented on a population level.

Current State of Breast Cancer Risk Reduction and Surveillance

Risk-based stratification in breast cancer screening is a widely understood concept. Clinical tools and existing guidelines are used to inform enhanced surveillance and risk reducing options for at-risk women. Other than being female, age is the primary risk factor for developing breast cancer and is the justification for age-based screening mammography guidelines (while breast cancer occurs in males, it represents fewer than 1% of all cases). Regular access to mammography screening has contributed to a substantial decrease in breast cancer associated mortality.[7] A wide distribution of invasive breast cancer diagnosis occurs between the ages of 40 and 70, leading to discrepancies in age-based recommendations between medical bodies. These discrepancies raise important questions: When is it appropriate to screen early?

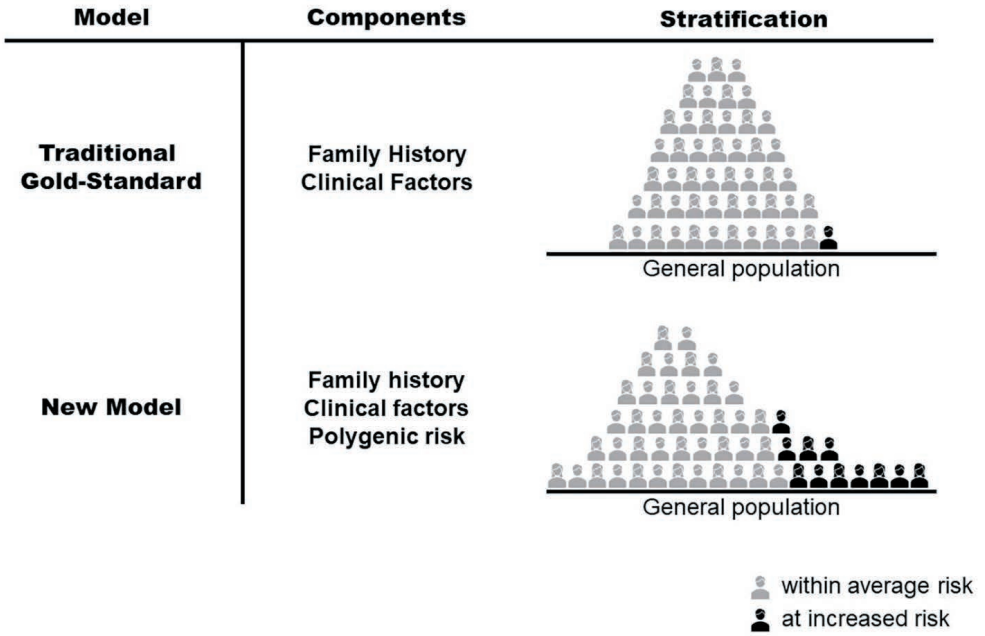

Figure 1: Side-by-side representation of clinical risk assessment models. Improved stratification of the asymptomatic, general population compared to traditional gold-standard risk assessment using a nested case/control dataset from the Nurses' Health Study to show a 9-fold difference between at-risk women identified by the traditional gold-standard (IBISv7) compared to the polygenic-integrated risk model (geneType); 2.5%, 22.4% respectively. At (increased) risk defined by a woman's absolute risk score greater than 20% remaining lifetime risk. Black figures represent proportion of women at increased risk of developing breast cancer. Grey figures represent the women within average risk.

Should population screening begin at 40,[8,9] 45[10] or 50?[11] How do we balance economic and health benefits?

Currently, family history and mammographic density are the two major risk factors that enable further stratification of screening-age women. Although family history carries weight in assessing breast cancer risk, *the majority of diagnoses occur in women without a family history of breast cancer, underscoring the limited utility of this risk factor in the general population.* And, although mammographically dense tissue can be identified in 43% of screening-age women, no standard recommendations exist for supplemental screening.[12] As we continue to identify more markers of risk, these tools will continue to be enhanced and the predictive ability of risk assessment will improve.

Improving on the Current State

Traditional gold standards in risk assessment include a variety of clinical models to calculate actionable absolute risk for either 5-year or remaining lifetime from the time of diagnosis. Some of these models were developed for the general female population, such as the Breast Cancer Risk Assessment Tool[13] and Breast Cancer Surveillance Consortium[14] models, and others were developed for women with a family history, such as the IBIS[15] and BOADICEA[16] models.

More recently, geneType for breast cancer was developed to bridge the gaps in risk assessments – a model that goes beyond clinical risk factors to include polygenic risk and mammographic density risk and has been designed to be used by any woman who may be currently considered to be at general population risk. The geneType model incorporates the standard epidemiological risk factors (including age, family history, menopausal status and body mass index) – but what provides improved population-level discrimination is the incorporation of mammographic density and polygenic risk.

When creating the geneType model, care was taken to reduce the amount and complexity of information a clinician would have to input into a model while still improving upon current risk stratification models. First, truncated pedigree is used to assign familial risk thereby enabling the model to capture necessary family history without hampering clinician time-management. Second, simple mammographic density Bi-RADS notification descriptors can be used if percentage density measurements are not readily accessible. Third, a simple saliva tube is used to collect the woman's DNA for genotyping. This is the most reliable factor that is not affected by patient recall or clinical record integration challenges.[17-19] The additional risk factors (age, menopausal status, height, and weight) require limited effort to collect.

Our data show that the geneType model outperforms the traditional gold standard models due to three measures: broader data types included in model; improved calibration; and discrimination between affected and unaffected women (two manuscripts in preparation). When we compared the geneType model to the traditional gold standard in a prospective cohort (UK Biobank) and in a nested case–control (Nurses' Health Study), we find the estimated increase in the number of at-risk women identified by geneType is increased by a factor of 4 and 9, respectively, in the two cohorts. The significant net re-classification compared to traditional gold standard models allows clinicians to identify more women at increased risk of developing breast cancer based on current risk thresholds. A cohort limitation of the first dataset led to constructive and applicable clinical observations; despite limited family history and no breast density data in the UK Biobank cohort, the geneType model still outperformed the gold standard. In this case, the missing data in the UK Biobank represents a common clinical scenario where breast density and full family history are often unavailable for the patient. In the Nurses' dataset, with no missing data, the model performed even better compared to the gold standard (**Figure 1**).

Actionable Clinical Outcomes

Risk assessment is not a diagnostic tool, nor will there ever be a simple positive or negative result. The risk score is the percent chance of the woman developing breast cancer over a given period, specifically, over the next five years and over one's lifetime (**Figure 2**). These two periods are used to consider different risk-reducing strategies and increased surveillance options.

Five-year Risk Score Thresholds

The United States Preventive Services Task Force[a], the American Society of Clinical Oncology[b], and the National Comprehensive Cancer Network[c] all have risk-reducing medication recommendations set around the five-year risk scores of 3%,[20] 3%,[21] 1.66%,[9] respectively. Above these thresholds, the benefits of chemoprevention outweigh the risks and results in a 35–65% reduction in breast cancer incidence, depending on the selective estrogen receptor modulator or aromatase inhibitor chosen.[22-24] In addition to risk-reducing medication, the guidelines[9] also discuss options to modify breast cancer screening for at-risk women.

a. U.S. Preventive Services Task Force, https://www.uspreventiveservicestaskforce.org/uspstf/

b. American Society of Clinical Oncology, https://beta.asco.org/

c. National Comprehensive Cancer Network, https://www.nccn.org/

Lifetime Risk Score Thresholds

The American Cancer Society,[d] American College of Radiology,[e] American Society of Breast Surgeons,[f] and National Comprehensive Cancer Networkc all have breast cancer screening recommendations set around the lifetime risk score of 20%.[8,25-27] Above this threshold, a woman qualifies for supplemental screening options such as MRI.

d. American Cancer Society, https://www.cancer.org/

e. American College of Radiology, https://www.acr.org/

f. American Society of Breast Surgeons, https://www.breastsurgeons.org

Incorporating Risk Assessment into Clinical Practice

Despite a multitude of medical bodies with screening and risk-reduction guidance available, few women are actually risk-assessed in clinical practice. This may, in part, be due to a disconnect between specialists and general practice care where the specialist bodies release recommendations that many primary care providers are not aware of or do not know how to put into practice due to lack of support (assay availability, clinical support tools) or reimbursement issues (further details in succeeding paragraphs). It must be kept in mind that primary care providers have a large number of patients with chronic and acute care needs and a limited amount of time per patient at an annual wellness visit.[28]

Facilitating disease risk prediction measures in the wellness setting is paramount to enabling general practice care providers to engage in preventive medicine. The most common hurdles to clinical implementation include initial patient triage and post-assessment continuum of care. Clinician education and peer-to-peer support are the primary methods to address these hurdles. Many organizations are trying to simplify or streamline clinical workflow through custom software,[29] applications,[30] electronic medical record integration, (like CRA Health[31]) and even commercially outsourced patient navigation specialists, but the de-centralized US healthcare system makes these options difficult to implement at scale.

Our current healthcare system also makes it harder to close the loop of clinical care. More often than not, clinicians refer a patient to a specialist facility (e.g., a high-risk breast center, a breast imaging clinic, or a breast surgeon) and the original clinician does not receive follow-up information. Medical records often go unshared, while at other times contradicting clinical opinions between providers result in a lack of confidence by patients in our healthcare system and many women end up in limbo. In our experience, these gaps in the care continuum ultimately result in clinicians declining to risk-assess their patients because they do not want the burden, or medical liability, of navigating post-assessment care with their patient. Increasing clinician resources can only improve the incorporation of risk prediction in clinical care.

Decision-Making Discussions with the Healthy Patient

Many clinical recommendations incorporate statements about decisions being made based only on individualized risk, others suggest the patient and clinician should engage in joint decision-making processes.[32] Risk assessments are tools that aid in this shared decision-making process. A clinician has the opportunity to use a risk score, such as geneType, to communicate a patient's personal risk of developing disease. The simple risk report enables the clinician to communicate risk in a standard format, within the confines of clinically actionable thresholds. But the combination of risk factors incorporated into the model allows for the identification of patients who traditionally are considered to be at average risk. Ultimately, every patient's risk score must be discussed in the context of their medical history to provide the most informed recommendations during the shared decision-making discussion. This is the paradigm for personalized precision medicine – that is, the use of precision medicine in a personalized setting.

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Example patient discussion #1

A healthy woman, aged 53 years, has had eight previous mammograms. She has extremely dense breast tissue and her last two mammograms led to biopsies. The first biopsy was negative, and the second biopsy (a year later) showed atypical ductal hyperplasia. The primary care provider (PCP) discusses the woman's risk reducing options,

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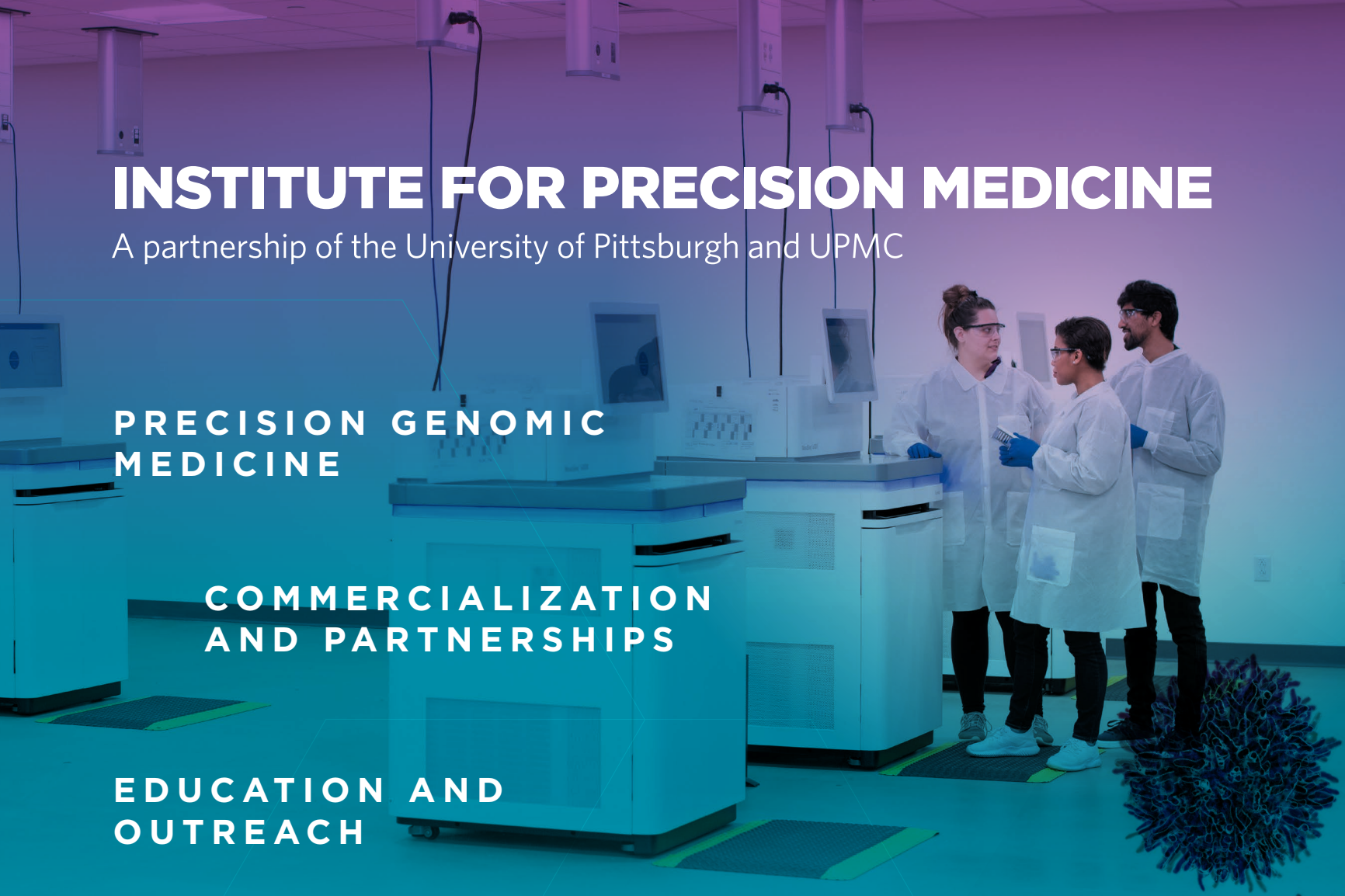

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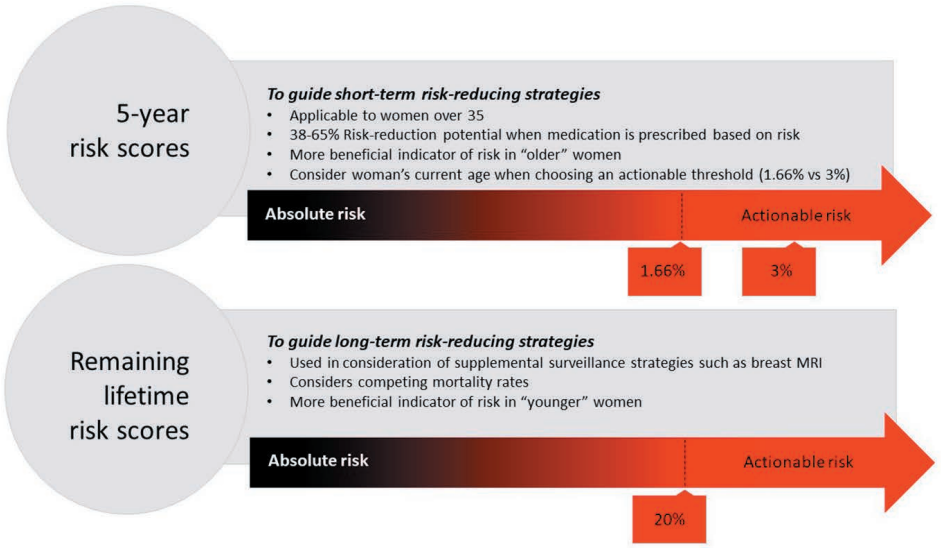


Figure 2: Clinical risk thresholds for breast cancer screening and risk-reducing medication recommendations. A short-term and long-term risk score can be calculated. Often due to age, a woman may be at increased risk with one, or the other. Risk-reducing strategies may be considered in the context of the woman's complete medical history.

including the option for chemoprevention.

The woman is not interested in the risk-reducing medication because she does not think she is at risk of breast cancer because she has no family history of breast cancer. The PCP offers her a risk assessment to continue the conversation with her. The woman's risk score comes back *increased*. [Note: this risk score does not include the risk associated with atypical ductal hyperplasia.] With this as context, the PCP is able to discuss the woman's risk of developing breast cancer, which is above average for a woman of her age. Despite being eligible for risk-reducing options based on her atypical hyperplasia, this patient was reluctant to commit to medication until she had the opportunity to better understand her risk of developing breast cancer. She and her PCP discussed the risk factors that she cannot change as well as those that she can change. Together, they initiated a plan to begin an aromatase inhibitor, which will reduce her risk by as much as 65%.[33] The PCP plans to monitor her side effects, including bone mineral density changes and hot flashes.

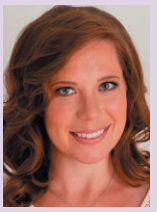
"Despite being eligible for risk-reducing options based on her atypical hyperplasia, this patient was reluctant to commit to medication until she had the opportunity to better understand her risk of developing breast cancer."

Example patient discussion #2

A healthy woman, aged 42 years, has no known family history of breast cancer, but she has limited contact with her relatives. She is nulliparous and recently had her first mammogram. She was found to have heterogeneously dense breasts and was consequently recalled – the subsequent mammogram and ultrasound results were normal, indicating a false positive initial screen. The patient's ordering clinician, her OB/GYN, was looking for options to give her. The patient was frustrated by the experience of a false positive result and wanted to know if she could be more active about her breast health. Her OB/GYN performed a clinical risk assessment using IBIS, which found that the woman was at higher-than-average risk but did not surpass a clinical threshold of risk. The OB/GYN subsequently ordered geneType, found that the woman was above the 20% lifetime risk threshold. The OB/GYN plans to order supplemental breast MRI for this patient. The OB/GYN also discussed the option of beginning risk-reducing medication in the next few years as an option for this patient after she finishes her in vitro fertilization journey.

Example patient discussion #3

A healthy woman, aged 52 years, had a mammogram at age 40, was told she had dense breast tissue, but has not had a mammogram in 12 years. She is very active and lives a healthy lifestyle and has no desire to get a mammogram because there are other health concerns that she worries about. Her PCP orders a risk assessment that shows her absolute risk of developing breast cancer is half that of women of her age. The PCP has the opportunity to suggest a compromise. The PCP schedules a mammogram for the



Erika Spaeth, PhD

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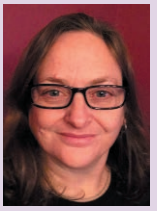
Dr. Spaeth is responsible for the development of clinical content and rationale behind geneType products. With a focus on transposing the company's cutting-edge approach to disease risk modeling into effortless yet actionable genetic-integrated information for both clinicians and patients, she is a cross-functional team member. She is involved in developing and executing commercial clinical research, pilot studies and managing academic research collaborations. She is also engaged in product development by aligning clinical development pathways to support commercial objectives. She has wide experience in the high complexity laboratory space from assay development to regulatory oversight of laboratory developed tests in the oncology, infectious disease and inherited disease space. Her postdoctoral training was completed at MD Anderson Cancer Center where she focused on the role of the microenvironment in tumor progression. Erika holds a Ph.D. in Biomedical Sciences from the University of Texas Health Science Center.

Richard Allman, PhD

Chief Scientific Officer, Genetic Technologies Ltd

Dr. Allman is the guiding force behind the genetic-integrated clinical risk assessment modeling, his team focuses on the development and validation of clinical commercial laboratory developed tests. With scientific and research experience in both the academic arena in the UK and the commercial sector in Australia, he has a diverse background in oncology research and translational medicine including drug development, diagnostics and assay design. He holds numerous patents in the area of clinical risk models. His research leadership, innovation management, and intellectual property strategy is integral to the commercial product development pipeline. Richard holds a Ph.D. in Microbiology from Cardiff University.



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Dr. Dite is an epidemiologist and biostatistician. She spent over 25 years in academic research before transitioning to the biotech sector. She is a leading expert in the management and statistical analysis of data from large and complex epidemiological studies. Integral in the company's R&D program, Dr. Dite overseas the algorithm development as well as the validation pipelines for current and future clinical risk models. She has published more than 129 papers in leading peer-reviewed journals. Gillian holds a PhD in Genetic Epidemiology from the University of Melbourne.

patient, but also engages with the patient in shared decision-making discussions around the option to reduce the screening frequency going forward. In addition, the PCP has the opportunity to discuss general breast cancer awareness as well as the benefits of healthy lifestyle habits cancer risk-reduction, regardless of risk status.

Preventive Healthcare is a Win for All

Disease screening tools such as mammograms have been proven to be effective and have reduced breast cancer mortality rates. A risk assessment tool such as geneType does not replace standard screening tools. Instead, it enables supplemental precision screening tools to be employed in at-risk groups. Importantly, standard clinical models do not discriminate well between affected and unaffected women.

In the examples above, we highlighted the clinical advantages of incorporating individualized risk assessment in shared decision-making discussions with patients. This type of personalized risk assessment encourages and empowers patient follow-through with preventive healthcare options. Using an improved risk stratification tool, there is a dramatic improvement in the discrimination between affected and unaffected women and the proportion of at-risk adults identified for supplemental options.

Ultimately, preventive healthcare leads to better medical outcomes at lower costs to the individual and the health system. Economic modeling has shown that geneType for breast cancer has resulted in a positive per-patient per-year saving. But even more important, when clinicians are better able to stratify their healthy patient population with geneType (vs standard model, publication pending), they can proactively identify those who would benefit from supplemental screening or other risk-reduction options; increase screening compliance; increase early-stage detection; and reduce the number of interval cancers). Most important, this net saving from using geneType risk stratification is a conservative estimate based on a low initial adoption rate among women aged 40–69 years and does not assume any reduction in standard of care screening – only increases to standard of care – as a result of risk assessment. JoPM

Summary points

- Disease screening and risk-reduction guidelines, for diseases such as breast cancer, require general population risk stratification.
- Large multiomic datasets are powerful tools that can be leveraged to refine clinical risk prediction models to improve risk stratification.
- Integration of a single-omic type (in the case of geneType, genomics) with standard epidemiological risk factors significantly improves general population risk stratification compared with clinical models.
- In an economic modelling scenario, we show a net savings per patient, per year as a result of more women getting screened, fewer interval cancers, and greater early-stage detection
- Establishing clinical support pipelines such as peer-to-peer resources and educational content is an important step in encouraging routine clinical implementation.
- More resources need to be allocated to close the loop on the continuum of clinical care. Especially with novel technologies, we have observed that our clinicians are spread too thin to keep up with advancements without the support need for patients to access personalized precision advancements and benefit from evolving standards of care.

References

1. Wand H, Lambert SA, Tamburro C, Iacocca MA, O'Sullivan JW, Sillari C, Kullo IJ, Rowley R, Dron JS, Brockman D et al: Improving reporting standards for polygenic scores in risk prediction studies. Nature 2021, 591(7849):211-9.
2. Hao L, Kraft P, Berriz GF, Hynes ED, Koch C, Korategere VKP, Parpattedar SS, Steeves M, Yu W, Antwi AA et al: Development of a clinical polygenic risk score assay and reporting workflow. Nat Med 2022, 28(5):1006-13.
3. Allman R, Dite GS, Hopper JL, Gordon O, Starlard-Davenport A, Chlebowski R, Kooperberg C: SNPs and breast cancer risk prediction for African American and Hispanic women. Breast Cancer Research And Treatment 2015, 154(3):583-9.
4. Allman R, Spaeth E, Lai J, Gross SJ, Hopper JL: A streamlined model for use in clinical breast cancer risk assessment maintains predictive power and is further improved with inclusion of a polygenic risk score. PLoS One 2021, 16(1):e0245375.
5. Dite GS, MacInnis RJ, Bickerstaffe A, Dowty JG, Allman R, Apicella C, Milne RL, Tsimiklis H, Phillips KA, Giles GG et al: Breast cancer risk prediction using clinical models and 77 independent risk-associated snps for women aged under 50 years: australian breast cancer family registry. Cancer epidemiology, biomarkers & prevention 2016, 25(2):359-65.
6. Starlard-Davenport A, Allman R, Dite GS, Hopper JL, Spaeth Tuff E, Macleod S, Kadlubar S, Preston M, Henry-Tillman R: Validation of a genetic risk score for Arkansas women of color. PloS one 2018, 13(10):e0204834.
7. Broeders M, Moss S, Nystrom L, Njor S, Jonsson H, Paap E, Massat N, Duffy S, Lynge E, Paci E et al: The impact of mammographic screening on breast cancer mortality in Europe: a review of observational studies. Journal of medical screening 2012, 19 Suppl 1:14-25.
8. The American Society of Breast Surgeons: Position statement on screening mammography. [https://www.breastsurgeons.org/docs/statements/Position-Statement-on-Screening-Mammography.pdf]; accessed July 2022.
9. NCCN: National Comprehensive Cancer Network. NCCN Cinical Practice Guidelines in Oncology. Breast Cancer Risk Reduction V1.2022.
10. American Cancer Society: Breast Cancer Early Detection and Diagnosis.; 2017. https://www.cancer.org/content/dam/CRC/PDF/Public/8579.00.pdf; accessed July 2022
11. Siu AL: Screening for Breast Cancer: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med 2016, 164(4):279-96.
12. Melnikow J, Fenton JJ, Whitlock EP, Miglioretti DL, Weyrich MS, Thompson JH, Shah K: Supplemental Screening for Breast Cancer in Women With Dense Breasts: A Systematic Review for the U.S. Preventive Services Task Force. Ann Intern Med 2016, 164(4):268-78.
13. Gail MH, Brinton LA, Byar DP, Corle DK, Green SB, Schairer C, Mulvihill JJ: Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. Journal of the National Cancer Institute 1989, 81(24):1879-86.
14. Tice JA, Bissell MCS, Miglioretti DL, Gard CC, Rauscher GH, Dabbous FM, Kerlikowske K: Validation of the breast cancer surveillance consortium model of breast cancer risk. Breast cancer research and treatment 2019, 175(2):519-23.
15. Amir E, Evans DG, Shenton A, Lalloo F, Moran A, Boggis C, Wilson M, Howell A: Evaluation of breast cancer risk assessment packages in the family history evaluation and screening programme. J Med Genet 2003, 40(11):807-14.
16. MacInnis RJ, Bickerstaffe A, Apicella C, Dite GS, Dowty JG, Aujard K, Phillips KA, Weideman P, Lee A, Terry MB et al: Prospective validation of the breast cancer risk prediction model BOADICEA and a batch-mode version BOADICEACentre. British journal of cancer 2013, 109(5):1296-301.
17. Brady LA, Tumiel-Berhalter LM, Schad LA, Bentham A, Vitale K, Norton A, Noronha G, Swanger C, Morley CP: Increasing Breast, Cervical, and Colorectal Cancer Screenings: A Qualitative Assessment of Barriers and Promoters in Safety-Net Practices. J Patient Cent Res Rev 2021, 8(4):323-30.
18. Polubriaginof F, Tatonetti NP, Vawdrey DK: An Assessment of Family History Information Captured in an Electronic Health Record. AMIA Annu Symp Proc 2015, 2015:2035-42.
19. Ozanne EM, O'Connell A, Bouzan C, Bosinoff P, Rourke T, Dowd D, Drohan B, Millham F, Griffin P, Halpern EF et al: Bias in the reporting of family history: implications for clinical care. J Genet Couns 2012, 21(4):547-56.
20. Force USPST, Owens DK, Davidson KW, Krist AH, Barry MJ, Cabana M, Caughey AB, Doubeni CA, Epling JW, Jr., Kubik M et al: Medication Use to Reduce Risk of Breast Cancer: US Preventive Services Task Force Recommendation Statement. Jama 2019, 322(9):857-67.
21. Visvanathan K, Fabian CJ, Bantug E, Brewster AM, Davidson NE, DeCensi A, Floyd JD, Garber JE, Hofstatter EW, Khan SA et al: Use of Endocrine Therapy for Breast Cancer Risk Reduction: ASCO Clinical Practice Guideline Update. J Clin Oncol 2019, 37(33):3152-65.
22. Fisher B, Costantino JP, Wickerham DL, Cecchini RS, Cronin WM, Robidoux A, Bevers TB, Kavanah MT, Atkins JN, Margolese RG et al: Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. Journal of the National Cancer Institute 2005, 97(22):1652-62.
23. Vogel VG: The NSABP Study of Tamoxifen and Raloxifene (STAR) trial. Expert review of anticancer therapy 2009, 9(1):51-60.
24. Cuzick J, Sestak I, Forbes JF, Dowsett M, Knox J, Cawthorn S, Saunders C, Roche N, Mansel RE, von Minckwitz G et al: Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial. Lancet (London, England) 2014, 383(9922):1041-8.
25. Monticciolo DL, Newell MS, Moy L, Niell B, Monsees B, Sickles EA: Breast Cancer Screening in Women at Higher-Than-Average Risk: Recommendations From the ACR. J Am Coll Radiol 2018, 15(3 Pt A):408-14.
26. Saslow D, Boetes C, Burke W, Harms S, Leach MO, Lehman CD, Morris E, Pisano E, Schnall M, Sener S et al: American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA: a cancer journal for clinicians 2007, 57(2):75-89.
27. Nccn: National Comprehensive Cancer Network. NCCN Cinical Practice Guidelines in Oncology. Breast Cancer Screening and Diagnosis V1.2022. In.; 2021.
28. Altschuler J, Margolius D, Bodenheimer T, Grumbach K: Estimating a reasonable patient panel size for primary care physicians with team-based task delegation. Ann Fam Med 2012, 10(5):396-400.
29. Settelmyer M AF: Case study: implementing high-risk cancer screening and genetic counseling in the community setting. . In: Association of Community Cancer Centers (ACCC) 45th Annual Meeting & Cancer Center Business Center Summit,: March 20-22, 2019.; Washington, DC.
30. Nazareth S, Hayward L, Simmons E, Snir M, Hatchell KE, Rojahn S, Slotnick RN, Nussbaum RL: Hereditary Cancer Risk Using a Genetic Chatbot Before Routine Care Visits. Obstet Gynecol 2021, 138(6):860-70.
31. Laws A, Mulvey TM: Implementation of a High-Risk Breast Clinic for Comprehensive Care of Women With Elevated Breast Cancer Risk Identified by Risk Assessment Models in the Community. JCO Oncol Pract 2021, 17(2):e217-e25.
32. Davidson KW, Mangione CM, Barry MJ, Nicholson WK, Cabana MD, Caughey AB, Davis EM, Donahue KE, Doubeni CA, Kubik M et al: Collaboration and Shared Decision-Making Between Patients and Clinicians in Preventive Health Care Decisions and US Preventive Services Task Force Recommendations. Jama 2022, 327(12):1171-6.
33. Cuzick J, Sestak I, Forbes JF, Dowsett M, Cawthorn S, Mansel RE, Loibl S, Bonanni B, Evans DG, Howell A: Use of anastrozole for breast cancer prevention (IBIS-II): long-term results of a randomised controlled trial. Lancet 2020, 395(10218):117-22.