

Concepts of Precision Medicine in Breast Cancer

An Expert Interview with Eleni Andreopoulou

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Dr Eleni Andreopoulou is an Associate Professor of Medicine and the Director of Breast Cancer Clinical Research at Weill Cornell Medicine and New York-Presbyterian Hospital, New York, NY, US, where she specializes in the care and treatment of patients with breast cancer. She is also a member of the Englander Institute for Precision Medicine at Cornell. She previously held faculty positions at the Albert Einstein College of Medicine and Montefiore Medical Center, New York, and the University of Texas MD Anderson Cancer Center, Houston, Texas, US. Dr Andreopoulou completed her training in major academic institutions in both Europe and the US, including St Bartholomew's Hospital and the Royal Marsden Hospital and Institute of Cancer Research in London, UK, and the New York University School of Medicine. She was a European Society of Medical Oncology fellow and was also awarded the Calabresi Scholarship in mentored cancer therapeutics. Dr Andreopoulou has a special interest in the individualization of patient treatment, particularly in caring for women with aggressive breast cancer. Her main research interest involves precision medicine to fast-track the drug development of biologics and targeted therapy to effectively manage, treat and cure breast cancer. She is involved with all phases of clinical drug development and especially focuses on innovative preoperative clinical trial design that incorporates cutting-edge technology. Dr Andreopoulou's research involves projects focused on pharmacogenomics predictors of response to treatment for early and advanced stage breast cancer. Dr Andreopoulou is an active investigator of several clinical trials of novel therapeutic approaches in advanced disease, including her leadership role as a principal investigator in the development of drugs sponsored by the Cancer Therapy Evaluation Program at the National Cancer Institute. Dr Andreopoulou actively facilitates the interface between basic and applied research at the Meyer Cancer Center at Weill Cornell Medicine. She leads a multidisciplinary, prospective breast cancer biobank to provide a crucial foundation for precision medicine research. Dr Andreopoulou has also been active with breast cancer awareness programs covering screening and prevention with a particular focus in serving underserved minorities in the local area. She has published several peer-reviewed articles, reviews, editorials and book chapters. She is a member of the American Society of Clinical Oncology, the American Association of Cancer Research, the American Women's Medical Association the Royal Society of Medicine in England, and the European Society of Medical Oncology.

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Q. Could you tell us a little about the latest research in organoids and biomimetic platforms in precision medicine?

Precision medicine aims to utilize information about a patient's tumor, including gene alterations that may aid in the identification of effective therapies.¹ Recent advances have allowed researchers to combine genomic analysis with *ex vivo* drug screens. The opportunity to develop preclinical models that retain the tumor's basic characteristics provides a platform for biomarker discovery and high-throughput drug screening. Patient-derived tumor xenografts have emerged as powerful systems to study many cancer types by growing tumor cells in immunocompromised mice. Advances in this area have focused on trying to improve engraftment rates and introduce the patient's own immune cells.² For more rapid and less costly screens, the patient's tumor cells are now also cultured in the laboratory in 3D as organoids, allowing us to screen thousands of candidate drugs and drug combinations that have the potential to be used in the clinic.³ The future of personalized medicine resides in being able to incorporate cells of the microenvironment in state-of-the-art biomimetic platforms. This method of screening will better account for the influence of the cells that are adjacent to the tumor, known to influence the growth of cancers and their response to treatment.⁴

Q. What role may artificial intelligence play in precision medicine?

Analysis of large data sets is a major driver in the development of precision medicine. Transforming big data into clinically-actionable knowledge can be a tedious process, requiring specialized personnel and efficient computational methods. Artificial intelligence (AI) and more specifically machine learning (ML) can play a key role in providing clinicians with faster access to medical data (*Precision Medicine Knowledge Base AI Bot* – WCM/NYP collaboration with Microsoft),⁵ better diagnostic tools,^{6,7} and drug discovery methods.⁸ Furthermore, integrating precision medicine data into electronic health records (EHRs)⁹ and applying AI and ML methods to EHRs will allow clinicians to better match patients to novel targeted therapies by exploiting the molecular vulnerabilities of their disease.

Q. How can we address the challenges related to security and privacy with personal health information?

In an era characterized by data breaches and the inappropriate sharing of personal information online, it is increasingly important to ensure that patient health and privacy information is adequately protected. Adhering to Health Insurance Portability and Accountability Act (HIPAA) guidelines and adopting the latest security standards is a great first step to ensure that both security and privacy with personal health information are protected. Building on top of HIPAA, the National Institute of Health’s All of Us Research Program¹⁰ (formerly known as Precision Medicine Initiative) has established the *PMI Privacy and Trust Principles*¹¹ and the *PMI Data Security Policy Principles and Framework*.¹² These principles promote transparency, respect of participant preferences, and describe in detail how data are shared, accessed, used, and how data quality and integrity is maintained. Furthermore, they outline how to protect, detect, respond to, and recover from a malicious attack from a third-party actor.

Q. What have neoadjuvant endocrine therapy studies taught us about the role of precision medicine in breast cancer?

Neoadjuvant endocrine therapy provides a unique opportunity to study endocrine-sensitive and -resistant breast cancer with hormone receptor-positive phenotype. This setting is gaining traction for accelerated development of effective therapy allowing integration of biomarkers and surrogate endpoints into the process of care for tumors that exhibit endocrine therapy resistance. Molecular testing at diagnosis to define the genetic “fingerprint” and accompanying molecular dependencies of the tumors we seek to eliminate, followed by longitudinal assessments of both clinical and biomarker responses, allows for patient selection to enroll in novel clinical trials exploring the impact of agents that aim to enhance response beyond that of endocrine treatments alone. From the precision medicine standpoint several lessons have been learned: the slow emergence of downstaging is relating to lower rate of apoptosis with endocrine therapy and dependence of response on the antiproliferative effects of estrogen deprivation. While change in Ki67 is accepted as a validated endpoint for comparing endocrine neoadjuvant agents, on-treatment levels of Ki67 are related to long-term prognosis more closely than pretreatment Ki67. The Preoperative Endocrine Prognostic Index (PEPI) combines residual Ki67 score with measures of on-treatment estrogen receptor (ER) and other clinicopathologic factors and has clinical utility. Preliminary studies demonstrate that tumors that exhibit aromatase inhibitor resistant proliferation in the neoadjuvant setting is

often sensitive to cyclin-dependent kinase inhibitor (CDKI) CDK4/6i. Serial Ki67 monitoring before surgery is therefore the logical approach to tailored use of adjuvant CDK4/6i treatment.¹³ Recent data demonstrated more pronounced treatment effect with the phosphoinositide 3-kinase (PI3K) selective inhibitor in the PIK3CA-mutated hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer.¹⁴ Suppression of proliferation is a pharmacodynamic indicator of response, but possibly not the only one in the ER signaling pathway. A more comprehensive study of residual disease will elucidate the constitute of response. Although many challenges remain to be addressed, the implementation of molecular testing has introduced new possibilities for informing precision medicine decisions. The Trial of Perioperative Endocrine Therapy – Individualizing Care (POETIC) is ongoing (NCT02338310).¹⁵

Q. How can precision medicine address the challenge of intra-tumor heterogeneity resulting from clonal evolution of the disease?

Advances in genetic sequencing analysis are helping to illuminate the prevalence of intra-tumor heterogeneity, which allows us to answer compelling high priority clinical questions. Intra-tumor heterogeneity refers to cellular diversity attributed to genetic and epigenetic factors, and to non-hereditary adaptive responses to selective pressures through the dynamic evolution of cancerous clones. Intra-tumor heterogeneity poses significant challenges and rationalizes differences in response to treatment.¹⁶

Precision medicine aims to decode the intra-tumor heterogeneity.¹⁶ The opportunity to define and re-define the molecular signature of a given tumor at multiple time points along its evolutionary lineage enables an understanding of the clonal evolution of tumors. Beyond untreated tumors, the ability to perform whole exome sequencing and clonality analysis of metastatic tumors is crucial to detect potentially actionable mutagenic divergence due to dynamic clonal evolution through the natural course of the tumor and treatment effect. The recent development of single-cell sequencing tools allows the transcriptomes of thousands of cells to be processed simultaneously in order to identify subpopulations of cells and provide functional insights.^{17,18} Understanding how tumors that are inherently chemoresistant and hard wired to migrate and invade as well as treatment influence in directing the evolution of different subclones is a compelling question with significant clinical implications, and its answer will allow therapy to be tailored to a changing tumor and its microenvironment. In this setting we clinicians work very closely with our scientist colleagues at the Englander Institute of Precision Medicine at Weill Cornell (<https://eipm.weill.cornell.edu>). □

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