Maine Cancer Genomics Initiative (MCGI) Forum

Building Bridges through Genomic Medicine

April 5 – 7, 2019

Samoset Resort, Rockport, Maine

PRESENTED BY
THE JACKSON LABORATORY
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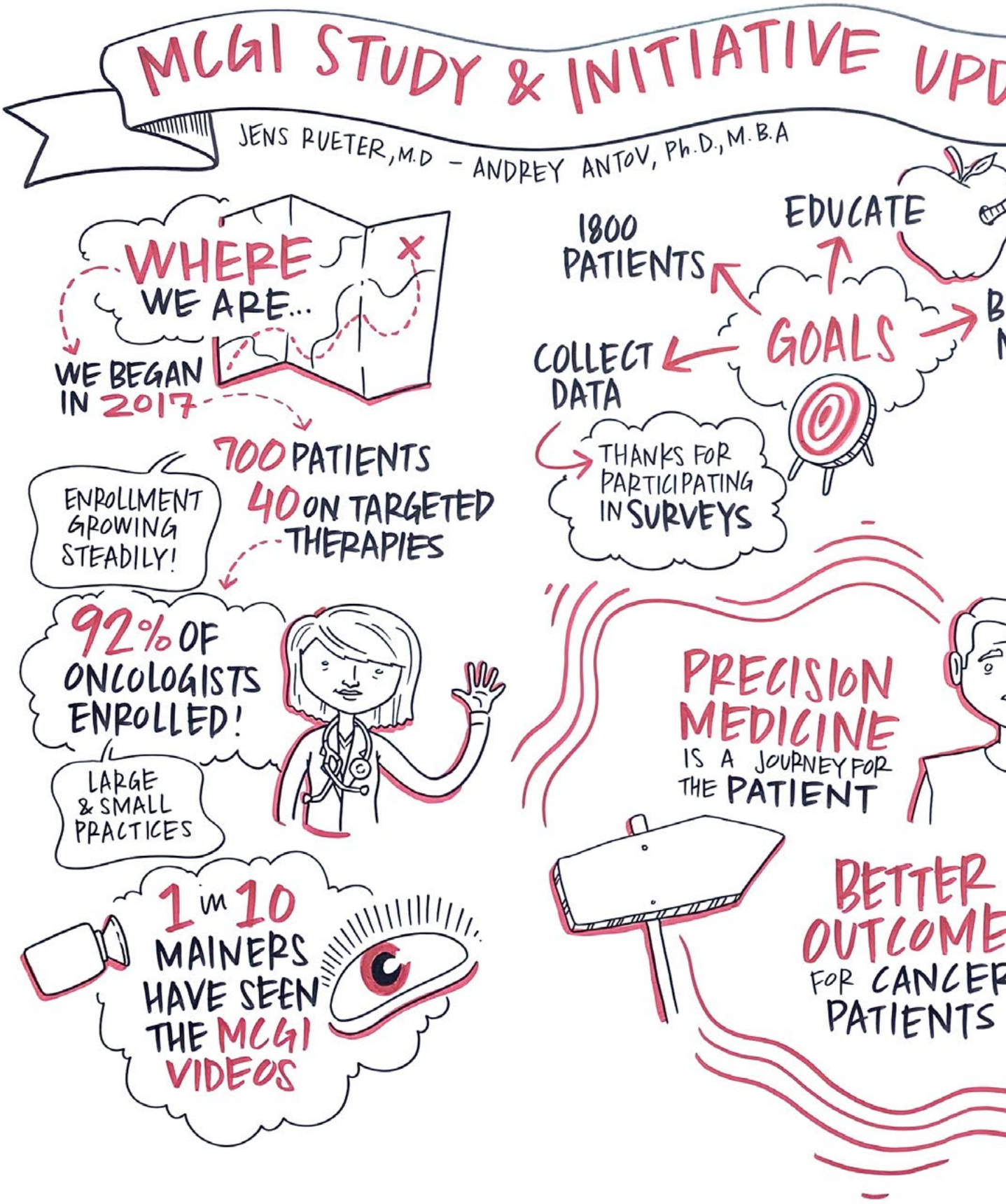
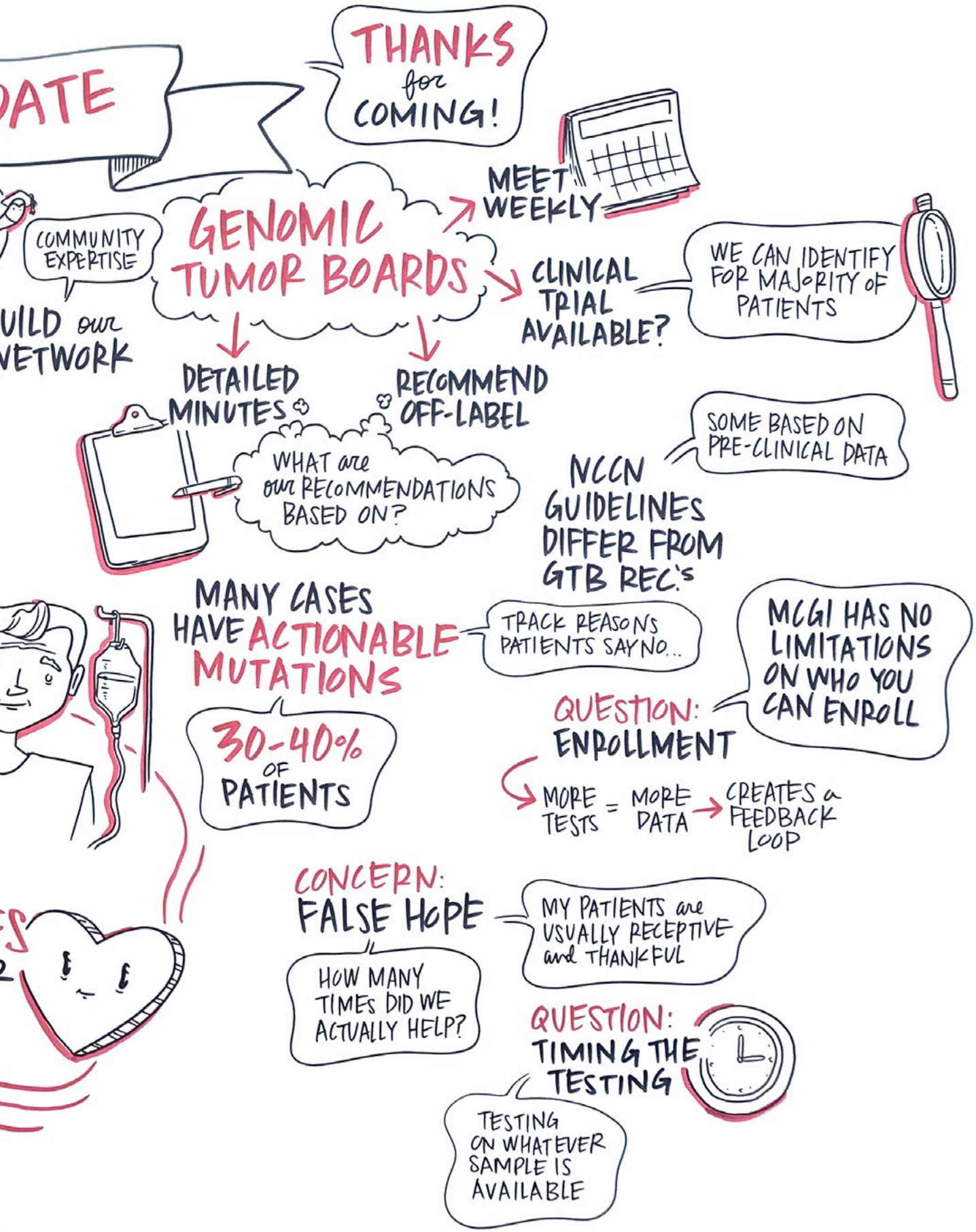

MCGI STUDY & INITIATIVE UPD
JENS RUETER, M.D - ANDREY ANTOV, Ph.D., M.B.A
WHERE WE ARE...
WE BEGAN IN 2017
700 PATIENTS
40 ON TARGETED THERAPIES
ENROLLMENT GROWING STEADILY!
92% OF ONCOLOGISTS ENROLLED!
LARGE & SMALL PRACTICES
1 IN 10 MAINERS HAVE SEEN THE MCGI VIDEOS
1800 PATIENTS
EDUCATE
GOALS
COLLECT DATA
THANKS FOR PARTICIPATING IN SURVEYS
PRECISION MEDICINE IS A JOURNEY FOR THE PATIENT
BETTER OUTCOME
FOR CANCER PATIENTS


DATE
THANKS for COMING!
MEET WEEKLY
COMMUNITY EXPERTISE
GENOMIC TUMOR BOARDS
UILD our VETWORK
CLINICAL TRIAL AVAILABLE?
WE CAN IDENTIFY FOR MAJORITY OF PATIENTS
DETAILED MINUTES
RECOMMEND OFF-LABEL
WHAT are our RECOMMENDATIONS BASED ON?
SOME BASED ON PRE-CLINICAL DATA
NCCN GUIDELINES DIFFER FROM GTB REC.'s
MANY CASES HAVE ACTIONABLE MUTATIONS
TRACK REASONS PATIENTS SAY NO...
MCGI HAS NO LIMITATIONS ON WHO YOU CAN ENROLL
30-40% OF PATIENTS
QUESTION: ENROLLMENT
MORE TESTS = MORE DATA → CREATES a FEEDBACK LOOP
CONCERN: FALSE HOPE
MY PATIENTS are USUALLY RECEPTIVE and THANKFUL
HOW MANY TIMES DID WE ACTUALLY HELP?
QUESTION: TIMING THE TESTING
TESTING ON WHATEVER SAMPLE IS AVAILABLE

MCGI Forum Summary

From Concept To Reality

Establishing a statewide medical program that reaches into remote rural areas and across healthcare systems is a formidable challenge. When the Maine Cancer Genomics Initiative (MCGI) launched three years ago, its goal was to bring the latest genomic testing and targeted treatments to all Maine cancer patients. It was the first large-scale effort of its kind in the U.S., and as such, MCGI had to overcome challenges not previously addressed elsewhere. It is still unique, but instead of being just a promising concept, MCGI is now an important part of everyday cancer care in Maine. The third annual 2019 MCGI Forum at Samoset Resort showcased the impact it's already had as well as forecasted an even greater future role for precision oncology in Maine and beyond.

The Forum brought oncologists, researchers and others from a wide variety of healthcare fields to discuss a number of topics associated with MCGI and precision oncology. It is an exciting time in oncology in general with the advent of immunotherapies as well as a growing arsenal of therapies that target specific oncogenic pathways, and providing hope for patients who may have previously run out of options. The Forum theme, "Building Bridges Through Genomic Medicine," captured the role of MCGI in connecting the latest research findings with cancer care throughout Maine. The bridges connect clinicians and their patients to the coming wave of research findings that have the potential to tailor therapies still further to benefit larger numbers of patients with fewer adverse effects.

The success of MCGI to this point is clear from the latest numbers. At the time of the Forum, every oncology practice in Maine was participating in MCGI, with 92% of the practicing oncologists on board. Nearly 700 patients were enrolled, and 162 had their cases reviewed by the Genomic Tumor Board. In 2018, there was a buzz at the Forum that the first patients had been referred to a clinical trial based on the results of their tumor testing and Genomic Tumor Board recommendations. In early 2019 that number exceeded 40 and is increasing at a steady pace.

While patient benefit underlies all of MCGI's activities, the program itself must be multi-faceted to deliver more treatment options and, ultimately, better care. A vital component is education for both patients and physicians regarding what genomic testing is, what information it provides, and what can be expected once the testing and analysis are complete. There is the genomic test itself, the JAX ActionSeq™ Plus Assay, which is now in its second version and reports on 209 genes in less than two weeks. The Clinical Genomics laboratory at JAX, which performs the assay, is now also a designated NCI-MATCH laboratory (the National Cancer Institute's *Molecular Analysis for Therapy Choice)*, meaning that it can provide testing and data analysis for NCI's MATCH precision medicine clinical trial. Finally, MCGI is working with the Center for Outcomes Research & Evaluation at the Maine Medical Center Research Institute to measure and study clinician and patient experiences and outcomes with genomic tumor testing and MCGI moving forward.

The TAPUR™ Study: Learning from Precision Medicine in Practice

Keynote Lecture
Richard Schilsky, M.D., FACP, FSCT, FASCO
Senior VP and CMO, American Society of Clinical Oncology

The advent of targeted cancer therapies has been somewhat slowed by traditional clinical trial design. Think about phase III trials, the traditional final step — there are usually two randomized patient groups, one that receives the experimental treatment and the other a control (usually the standard of care treatment at the time). But with a targeted therapy, it is known that only a subset of patients will benefit, so stratifying, not randomizing, patients is important. And in advanced cancer, the "standard of care" is often known to have minimal or no efficacy. New thinking is clearly needed.

In his keynote presentation, **Richard Schilsky** presented the Targeted Agent and Profiling Utilization Registry (TAPUR™) Study, an initiative from the American Society of Clinical Oncology (ASCO) that he has spearheaded to help address the challenges involved with bringing targeted therapies to market. TAPUR's goals are complementary to those of MCGI: to provide targeted therapies to patients with an identified druggable genomic variant and to learn from the real-world practice of prescribing these targeted therapies to patients. The study is large in scope, both in terms of participating clinical sites — 120 in 22 states — but also in that it is testing 16 different compounds or combination therapies for a large number of genomic aberrations in a variety of tumor types.

An eligibility requirement is genomic testing results from a clinical laboratory, that meet treatment specific inclusion/exclusion criteria. The other important stipulation is that patients have advanced cancers with no standard treatment options available. Once the patient is considered by the treating clinician, the patient can be screened for the study. If the match of genomic test result and targeted therapy isn't perfect, a molecular tumor board weighs in on the treatment options based on tumor genomics. Ultimately, about 50% of those referred to the board enroll in a TAPUR study arm. As of the time of the Forum, there were 1,941 patients registered and 1,398 enrolled, with many completed patient cohorts.

Future plans call for adding an immune checkpoint inhibitor in combination with targeted therapies — an innovative new treatment approach for certain patients. Also, like MCGI, TAPUR is studying its participating physicians' use, attitudes and perceptions of tumor genomic testing. Overall, Schilsky asserted that the direct benefits of TAPUR go well beyond the patient and physician. The pharmaceutical industry is learning about the use and outcomes of their drugs, payers receive data to inform coverage decisions, and regulators receive insight on off-label drug use and safety. In addition, TAPUR is providing a new way to structure and analyze clinical trials in the rapidly changing cancer treatment field.


MD reviews results of genomic test performed in CLIA certified/CAP accredited lab
Patient registered on study
MD determines if drug match exists in protocol or appropriate for MTB review
Patient enrolled on study
No match, Rx at MD discretion
Matched therapy administered; safety and efficacy outcomes recorded
Data monitoring committee regularly reviews outcomes of tumor-variant-drug groups
Results released when protocol-specified endpoints met
15

Pathology and Utilization of Assays

Oncologists working with MCGI are becoming more comfortable with ordering genomic tests for their patients as well as interpreting the results with the help of the tumor board. But what happens in between? How are the tests performed, what are the challenges involved and exactly what information do they provide? The first session of the morning provided answers to these questions and more.

The first talk, from **Christopher Gocke, M.D.**, of Johns Hopkins University, was fittingly titled "*Everything You Always Wanted to Know About NGS But Were Afraid to Ask.*" Actually, Gocke presented a pathologist's perspective of tumor cell analysis from visual assessment to NGS (Next-Generation Sequencing) to the emerging, and not-yet-standardized, assessment of tumor mutational burden to inform possible immunotherapy strategies. He pointed out that while identifying sequence variants has become relatively routine, the biological meaning of most variants remains unclear, presenting ongoing challenges for interpretation.

Marek Skacel, M.D., directs the molecular pathology laboratory at Dahl-Chase Diagnostic Services in Bangor, Maine, which provides NGS testing and analysis in a community healthcare setting. As such, his lab prioritizes clinical relevance, rapid turnaround and the ability to work with very small samples (e.g., less than 10 nanograms of DNA/RNA). Dahl-Chase provides testing for cancers including but not limited to lung and colon cancers, as well as a myeloid panel and reports results in close consultation with a molecular tumor board and ordering oncologists. Skacel emphasized the importance of communication among the entire medical group — oncologist, pathologist, surgeon, radiologist, and biopsy team — to obtain the best results.

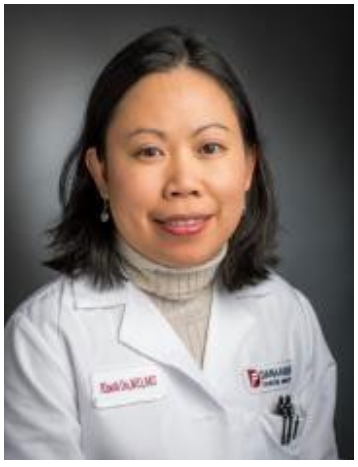
The Clinical Genomics laboratory at JAX has been working with MCGI participants to refine their cancer sample testing protocols. **Honey Reddi, Ph.D., FACMG**, who directs the lab, discussed the details of ActionSeq™ 2.0 Plus, the latest version of the assay. It now analyses 501 cancer associated genes, 209 of which are used for reporting of actionability, and can be used for tumor mutation burden and microsatellite instability reporting. The laboratory is now NCI-MATCH accredited. The NCI-MATCH trial accrues patients to treatments targeting CNVs, indels, and fusion variants in 17 genes.

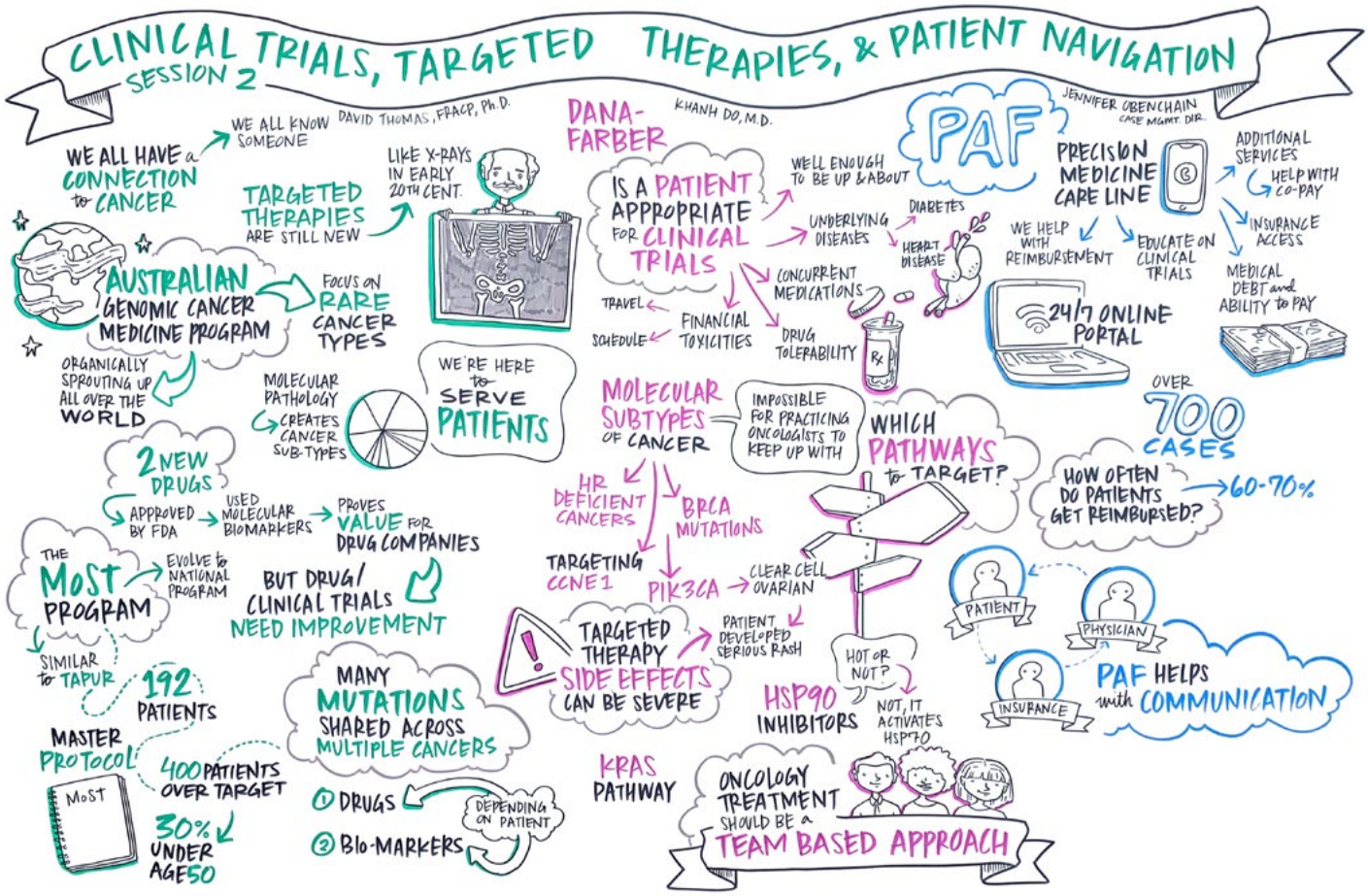
Clinical Trials, Targeted Therapies and Patient Navigation

Initiatives such as MCGI have large numbers of stakeholders with different perspectives, challenges, and needs. Administering them and providing data-based therapy guidance for patients in addition to delivering therapies, some of which are still early in the clinical trial process, requires working with all of them — not an easy task. The second Forum session provided insight into the delivery of therapies from a few of the perspectives, including that of a patient advocate.

To implement a nationwide program similar to MCGI in Australia, **David Thomas, FRACP, Ph.D.**, faces a much larger scope in every way. Pharmaceutical companies have disinvested in Australia for decades, and the clinical trial participation across all cancers stands at a mere 7%. Implementing biomarker-driven precision oncology trials for rare cancers demands creativity, so Thomas and colleagues launched the Cancer Molecular Screening and Therapeutics (MoST) program to drive efficiency and access using an innovative signal-seeking clinical trial design. Working under the auspices of the Australian Genomic Cancer Medicine Program, an organization of the major cancer centers in every state and territory, the program will screen more than 5,000 Australians with advanced cancer and treat more than 600 in trials.

Closer to home, **Khanh Do, M.D.**, from the Dana-Farber Cancer Institute addressed a crucial step once genomic testing and analysis is complete: finding the right clinical trial for patients based





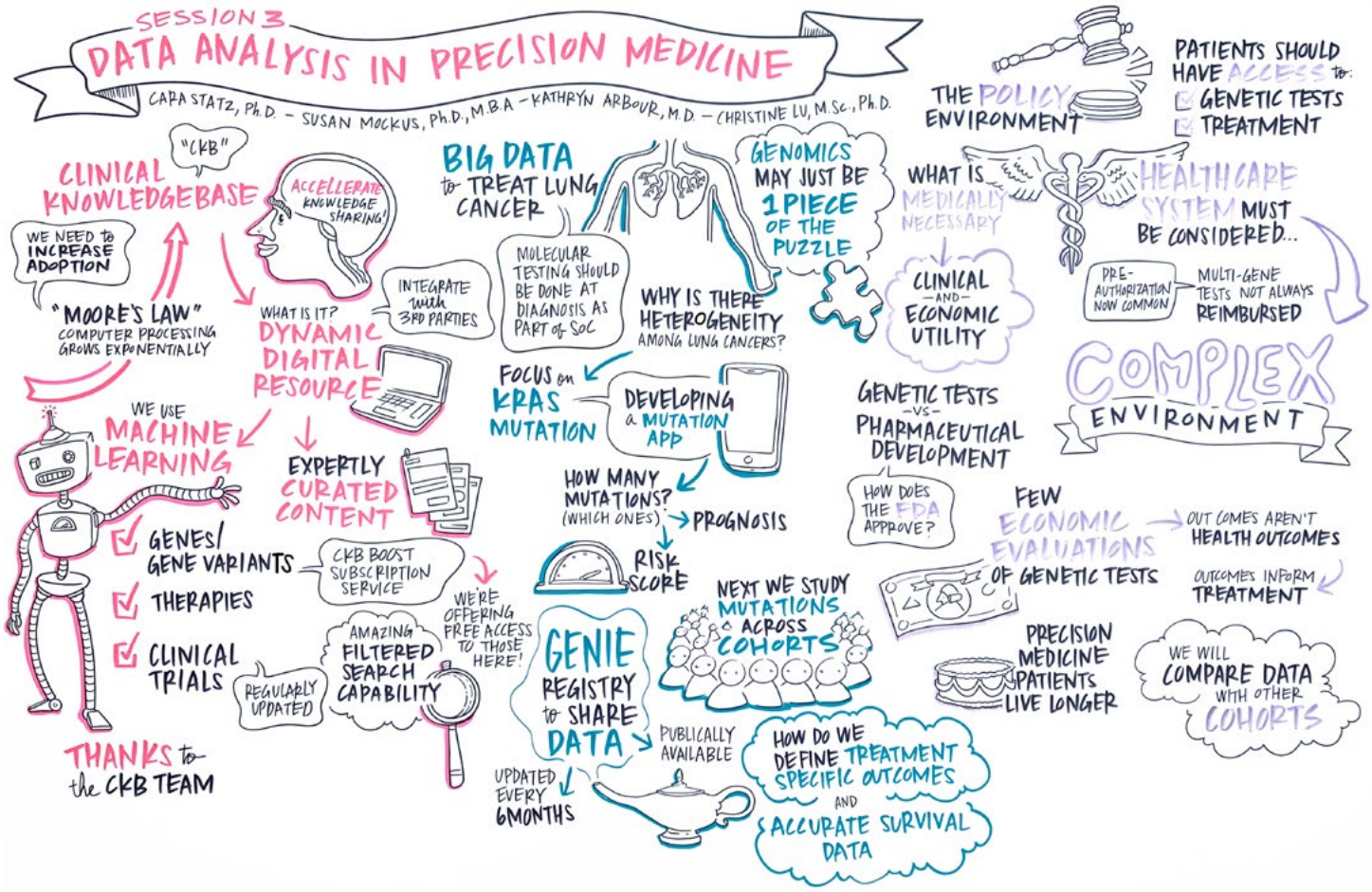
on their test results. In addition to matching available trial drugs with the genomic lesions in the tumor, the process must take into account logistics including travel and added costs, and other patient data such as co-morbidities and concurrent medications. Ultimately, matching a patient with the right clinical trial comes down to their goals of care. Do also provided several successful examples of matching ovarian cancer patients with a variety of targeted therapies depending on the test results.

Figuring out appropriate goals of care and deciding on the right course of action to achieve them is a daunting task, especially for patients already dealing with a very serious disease. Assistance is available, however, and **Jennifer Obenchain** from the Patient Advocate Foundation (PAF) presented her work to increase access to healthcare services and medications and help patients navigate the difficult financial and logistical issues that arise. MCGI has partnered with PAF to assist cancer patients in the program, particularly those that are under- or uninsured and/or have other challenges that limit access to care. To date PAF has supported more than 700 cases involving patients and doctors seeking access to treatment identified by genomic testing.

Data Analysis in Precision Medicine

What separates precision oncology from traditional oncology practice? More data about the patient and his or her cancer. With that data and the insights gained, targeted therapies and immunotherapies can be identified — or ruled out — improving the probability for response. But the cancer data continuum covers a wider spectrum, from research results to clinical utility findings, and all facets were addressed at the Forum's data session.

The genomic tests provided by MCGI are only clinically useful if they can identify the genes and genetic variants truly involved with cancer progression and maintenance. JAX's **Cara Statz, Ph.D.**, and **Susan Mockus, Ph.D., M.B.A.**, presented on the Clinical Knowledgebase (CKB), a digital resource developed at JAX that connects complex cancer genomic profiles to therapies and provides support for the variant interpretation process. Gathering data from multiple sources, from bioinformatics-based variant calls to pathology report diagnoses to patient data repositories and clinical trial results, CKB provides the latest information on the meaning of gene variants in cancer and therapy efficacy. As of the time of the Forum, CKB has been used by more than 50,000 people — 75% clinically based — from 140 countries.



Bringing the discussion directly into the clinic, **Kathryn Arbour, M.D.**, of Memorial Sloan Kettering (MSK) Cancer Center presented on the use of data in treating lung cancer. The treatment decision process currently includes multiple stages, including testing to identify driver mutations, and, if none are found, PD-L1 testing to assess the potential efficacy of checkpoint blockade-based immunotherapy. MSK is currently working on a genomic risk score, Oncocast, for individualized risk in the most common type of lung cancer (non small cell lung carcinoma) based on tumor mutation and co-mutation patterns. Preliminary Oncocast data show robust survival probability differences between the four risk score categories. Moving forward, they are participating in Project GENIE (*Genomics Evidence Neoplasia Information Exchange*), a collaborative effort led by the American Association of Cancer Researchers, to aggregate cancer genomic data with clinical outcomes to catalyze precision oncology.

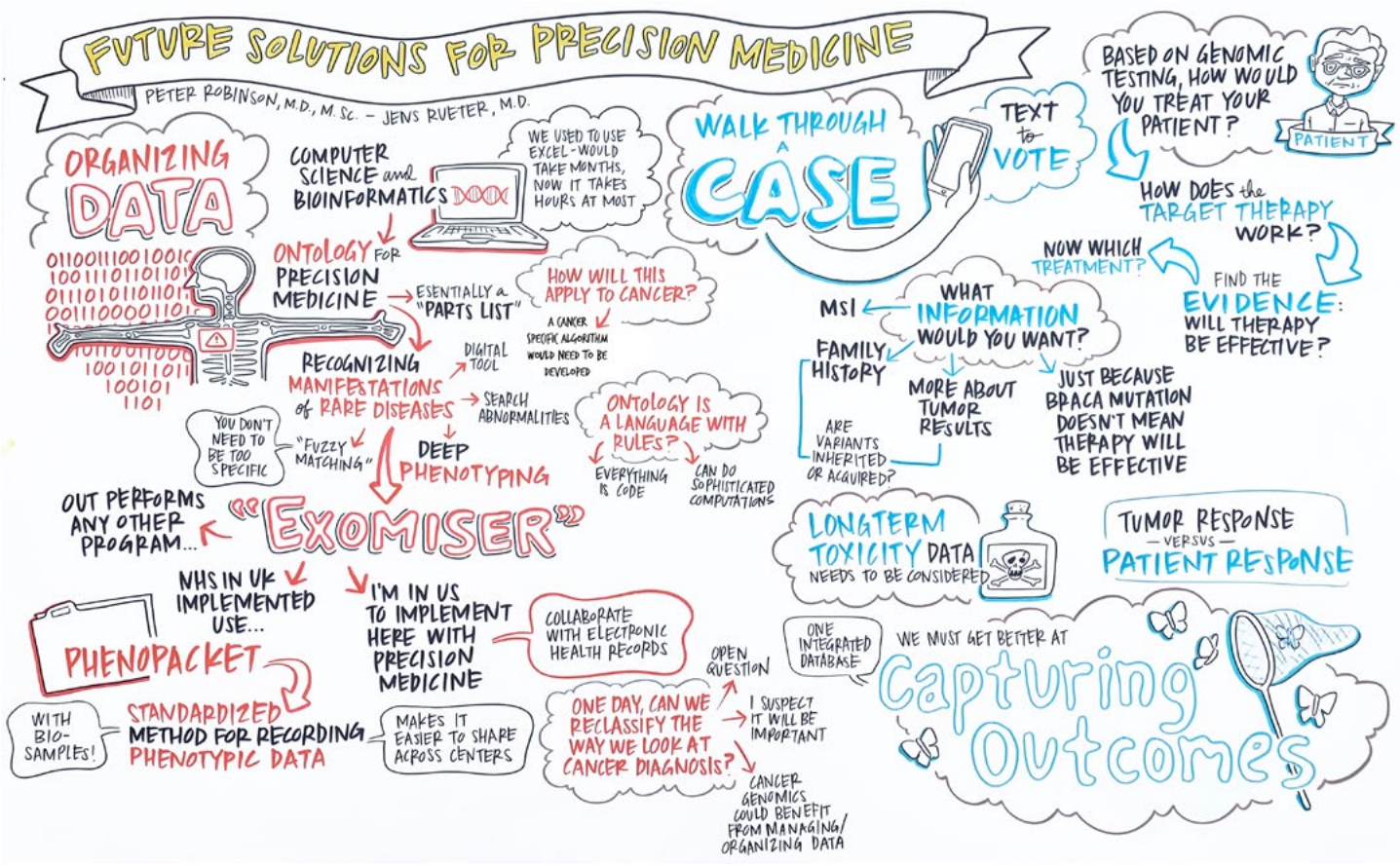
Fittingly, **Christine Lu, M.Sc., Ph.D.**, from the Department of Population Medicine at Harvard Medical School, wrapped up the session by presenting data about data. That is, she measures the results of using all of the data previously discussed to guide cancer therapy. Though the theoretical benefits are clear, there are still several challenges to wider real-world implementation of precision oncology, including questions about analytical and clinical validity, impact on clinical practice and overall patient benefit, and economic value. More data is therefore needed to answer the questions and indicate the best ways forward. Lu is leading a study into the clinical and economic utility of MCGI in particular, and the preliminary results are encouraging. So far, the data shows that patients participating in the program live longer and incur lower medical costs per day, providing evidence that programs like MCGI provide multiple patient benefits.

Future Solutions for Precision Medicine

MCGI has accomplished a great deal in a relatively short time frame. Precision medicine based on genomic data is now part of Maine cancer care, with benefits to patients that were previously unavailable locally. So where is MCGI, and the field of precision oncology as a whole, headed? The final session of the day contemplated next steps, both from research and clinical practice contexts.

JAX Professor **Peter Robinson, M.D., M.Sc.**, focused on the future of clinical data organization, arguing that precision medicine requires precision language. Current clinical terms are often not standardized, so mining insight from clinical phenotyping data is unnecessarily difficult, even when they can be extracted from electronic health records. The solution is to develop and implement a human phenotype ontology, which is a controlled terminology that invokes formal relationships between and among concepts, providing a type of description logic highly useful for computational analysis. Ontology relationships provide the ability to refine "fuzzy" phenotyping attributes with related terms that add specificity, leading to the identification of co-occurring traits and disease matching. Combining genome with ontology-based phenotype data provides a powerful discovery platform for generating genotype-phenotype relationships and arriving at clinical diagnoses.

During the day's final session, MCGI Medical Director **Jens Rueter, M.D.**, presented a real patient case and asked attendees how they would treat the patient based on the data provided. An expert panel also weighed in. The exercise provided a compelling example of how genomic testing-based treatment decisions are made. It also illustrated that more information and evidence, such as how each genetic variant in different cancers interacts with the mechanisms of action of the therapies, would provide clearer guidance in many cases. What can provide such evidence moving forward? Rueter discussed patient-derived xenograft (PDX) mouse models, which are being used as testing platforms to assess drug response with a large number of human tumors with different genetic variants. The models



provide a way to rapidly increase the number of variants tested, and the early results indicate that the responses seen in the mice do reflect patient responses. Integrating patient and research outcomes will inform care in the future by providing better and more comprehensive data from which to make treatment decisions.

In the Clinical Trials, Targeted Therapies and Patient Navigation panel session, **Catherine Del Vecchio Fitz**, a Maine native who now runs Precision Oncology Consulting, LLC and serves as a clinical trials expert on the MCGI genomic tumor board, highlighted the challenges surrounding clinical trial navigation for both providers and patients. She has seen significant evolution of the MCGI program since its inception, which has brought increased awareness of and access to clinical trials for cancer patients across Maine.

About the Maine Cancer Genomics Initiative

The mission of the Maine Cancer Genomics Initiative (MCGI) is to enable widespread access to clinical cancer genomic tests for the Maine oncology community and to increase the understanding of cancer genomics by Maine oncology clinicians.

MCGI is enabled through generous financial support from The Harold Alfond® Foundation and leverages the strengths of key medical and bioscience research institutions in Maine to create an alliance focused on precision cancer diagnostics and treatment.




The Maine Cancer Genomics Initiative is led from the MCGI Offices in Augusta, Maine. For more information about healthcare aspects of the Initiative contact Jens Rueter, MD. For information about business aspects contact Andrey Antov, PhD, MBA. For information about the MCGI-study contact Petra Helbig, CCRP. For information about the Genomic Tumor Board sessions and other MCGI events, such as the annual MCGI Forum contact Jennifer Bourne, MS. Email us at mcgi@jax.org; we look forward to hearing from you.

About The Jackson Laboratory

The Jackson Laboratory (www.jax.org) is an independent, nonprofit biomedical research institution with nearly 2,300 employees. Headquartered in Bar Harbor, Maine, it has a National Cancer Institute-designated Cancer Center, a facility in Sacramento, Calif., and a genomic medicine institute in Farmington, Conn. Its mission is to discover precise genomic solutions for disease and empower the global biomedical community in the shared quest to improve human health.

The Jackson Laboratory
Leading the search for tomorrow's cures

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