Maine Cancer Genomics Initiative (MCGI) Forum

Building Bridges through Genomic Medicine

April 6 – 8, 2018

Samoset Resort, Rockport, Maine

PRESENTED BY
THE JACKSON LABORATORY
WITH THE SUPPORT OF THE HAROLD ALFOND® FOUNDATION

Building Bridges Through Genomic Medicine

Maine Cancer Genomics Initiative (MCGI) Forum

April 6 – 8, 2018 Samoset Resort, Rockport, Maine

Table of Contents

The Jackson Laboratory

Leading the search for tomorrow's cures

Welcome to the second Maine Cancer Genomics Initiative (MCGI) Forum: Building Bridges Through Genomic Medicine. We are so pleased to see all the faces in this room — together, we've made tremendous progress over the last year.

We have:

- Created a unique, Maine-centric oncology network focused on improved care through genomic technology adoption
- Designed and approved an innovative study protocol that allows us to collect important data and measure results including patient outcomes and longitudinal clinician knowledge
- Opened the study at almost every single oncology practice in the state of Maine — a major accomplishment
- Enrolled more than 150 patients with more than 80 percent of Maine medical oncologists and oncology nurse practitioners on board already
- Run nearly 20 Genomic Tumor Boards.

And, as we'll learn during this year's forum, we're just getting started.

We have an exciting day of learning planned. We're going to hear about similar precision medicine programs and their application in clinical practice; we will discuss how MCGI can benefit your own practice and improve cancer care in Maine; and we'll share successes and challenges as a community.

Some of you may know that The Jackson Laboratory (JAX) has been part of the Maine community since 1929. As an NCI-designated basic science cancer center, traditionally our contributions have been focused in the lab. This is part of what makes MCGI such an exciting program. We are grateful for the chance to work directly with all Maine oncology practices and the Maine Medical Center Research Institute (MMCRI) to improve access and outcomes for Mainers with cancer. With your support and your dedication, we can change the game for our neighbors and friends and families touched by cancer. We can apply the rapidly developing field of precision medicine to accelerate its application in Maine, and, together, we can help our communities gain better outcomes after cancer diagnoses.

Thank you for your trust, support and dedicated partnership in this novel, state-wide, community precision medicine initiative. We look forward to continuing our work with you to bring new technologies to clinical practice and define new clinical pathways.

Best regards,

Jens Rueter, M.D., Medical Director, MCGI | The Jackson Laboratory
Andrey Antov, Ph.D., M.B.A., Program Director, MCGI | The Jackson Laboratory

www.jax.org
600 Main Street, Bar Harbor, ME 04609 | 207.288.6000

The Maine Cancer Genomics Initiative

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

Approximately 9,000 new cancer cases occur each year in Maine. Oncologists and other healthcare providers often struggle with identifying optimal therapies for many of these patients using conventional diagnostic methods and clinical guidelines. However, the combination of genetic mutations in a tumor — its molecular signature — may be much more indicative of the appropriate treatment. In addition, a rapidly increasing body of knowledge about genomics in cancer demonstrates significant promise for treatment of cancer of all types.

The mission of the 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. Specifically, the MCGI has four major goals. They are:

- To provide up to 1800 patients and their respective oncology clinicians in Maine with access to somatic cancer genomic tests and clinical reports from the CLIA-certified/CAP-accredited Clinical Genomics Laboratory.
- To advance the field of clinical genomics by increasing knowledge about the adoption and use of these tests in the Maine community oncology setting.
- To deliver educational programs in cancer genomics and precision medicine consisting of online educational modules and MCGI-organized and supported genomic tumor boards to Maine oncology clinicians.
- To build a research network for "Community Genomic Medicine" by establishing a collaborative Maine-wide research network of cancer providers and institutions and a mechanism to enable participation of rural practices in Maine in this network.

With The Jackson Laboratory's expertise in genomic sequencing, bioinformatics, cancer analytics and drug curation, the participation of healthcare professionals from Maine oncology and pathology practices, and financial support from The Harold Alfond® Foundation, MCGI continues the effort to bring world-class cancer care to Maine patients.

THE HAROLD ALFOND® FOUNDATION

Founded in 1950, The Harold Alfond® Foundation furthers the philanthropic legacy of Harold Alfond, the founder of Dexter Shoe Company and a longtime supporter of Maine communities in which he and his family worked and resided. Harold Alfond awarded matching challenge grants to organizations to build community partnerships and to inspire and leverage additional giving by others. He ensured that his philanthropy would live on by committing nearly all of his wealth to the Foundation, which continues to support charitable causes in the State of Maine.

Consistent with Harold Alfond's own giving pattern and philanthropic principles, the Foundation favors education, healthcare, youth development, and other selected charitable causes. The Foundation applies Harold Alfond's business approach to funding decisions, his belief in teamwork, and his love of competition by continuing to award matching challenge grants to projects that meet a demonstrable need, are entrepreneurial, promote teamwork, have measurable performance outcomes, are financially viable, and have quality management and board leadership.

THE JACKSON LABORATORY

We discover precise genomic solutions for disease and empower the global biomedical community in our shared quest to improve human health. At The Jackson Laboratory (JAX), we apply passion, innovation and ever-increasing precision to make this mission a reality. We are accelerating disruptive scientific breakthroughs tailored to the needs of individual patients and closing in on the genetic and molecular causes of disease. We also educate current and future scientists and empower the global biomedical community by providing critical resources, data, tools and services.

Founded in 1929, The Jackson Laboratory is an independent, nonprofit biomedical research institution with nearly 2,000 employees who are passionate about our mission: to discover precise genomic solutions for disease and empower the global biomedical community in the shared quest to improve human health.

JAX conducts mammalian genetics research and raises research mice in Bar Harbor, Maine; it has a new genomic medicine research laboratory in Farmington, Conn. which enables the Laboratory to translate its fundamental science into the clinic. And, it conducts contract research and raises research mice at its laboratory in Sacramento, California. The Laboratory is a National Cancer Institute-designated Basic Cancer Center and also has initiated a cancer research laboratory in Seoul, Korea.

The Jackson Laboratory has more than 60 principal investigators who come together from diverse backgrounds and areas of expertise to advance mammalian genetics and human genomics research in aging, behavioral disorders, bioinformatics, cancer, complex traits, developmental disorders, diabetes and obesity, eye research, genetics and genomics, immune disorders, infectious diseases, neurodegenerative and neuromuscular diseases, reproductive disorders, resource development and skin disease.

From high school summer programs to graduate and postdoctoral training to conferences that further the education of practicing scientists, physicians and professionals, The Jackson Laboratory advances science and improves health through our commitment to education.

JAX® Mice, Clinical & Research Services at The Jackson Laboratory is a global resource for developing, distributing and analyzing innovative models of human disease. It offers an array of model creation, husbandry and diagnostic and analytic services ranging from custom breeding and strain preservation to drug efficacy studies and genome sequencing, all focused on empowering basic scientific research and drug discovery.

Agenda

The April 2018 forum will focus on:

- Discussions on the integration of cancer genomics testing in clinical care
- Updates on the MCGI Study and Initiative
- Building a collaborative network of oncology healthcare providers to facilitate the growth of genomic medicine initiatives

Friday, April 6, 2018

3:00 P.M.	*Arrival and Check-in Begins*	*Resort Entrance*
4:00 P.M.	Steering Committee Meeting — *members only*	*Penobscot Bay*
5:00 P.M.	Reception	*Vinalhaven*
6:00 P.M.	**DINNER AND KEYNOTE**	*Vinalhaven*
	Introductions and Acknowledgments **Jens Rueter, M.D. | The Jackson Laboratory**	
	Opening Address **U.S. Senator Susan Collins | Welcoming Video Message**	
7:30 P.M.	*Break*	
8:00 P.M.	Informal Q&A **Edison T. Liu, M.D. | The Jackson Laboratory** **Chuck Hewett, Ph.D. | The Jackson Laboratory** **Jens Rueter, M.D. | The Jackson Laboratory** **Andrey Antov, Ph.D., M.B.A. | The Jackson Laboratory**	*Enoteca Lounge*

Saturday April 7, 2018

7:30 A.M.	*Breakfast*	*Vinalhaven*
8:20 A.M.	**OPENING REMARKS** **Jen Rueter, M.D. | The Jackson Laboratory** **Andrey Antov, Ph.D., M.B.A. | The Jackson Laboratory**	*North Haven*
	SESSION 1: The Promise of Precision Medicine **3.0 CME, 1.5pt MK MOC, 1.5pt PA MOC**	*North Haven*
8:30 A.M.	Update on the MCGI Study and Initiative **Jens Rueter, M.D. | The Jackson Laboratory** **Andrey Antov, Ph.D., M.B.A. | The Jackson Laboratory**	
9:00 A.M.	Identifying Features that Predict Outcome from Cancer Sequencing Data **Jeff Chuang, Ph.D. | The Jackson Laboratory**	
9:30 A.M.	New Genomic Signatures in Triple Negative Breast Cancer **Edison T. Liu, M.D. | The Jackson Laboratory**	
10:15 A.M.	*Break*	
10:30 A.M.	Breakout Session: Communicating with Patients About Cancer Somatic Testing **Paul Han, M.D. | Maine Medical Center Research Institute**	*Break out rooms: Penobscot Bay, Owl's Head, Spruce Head*
12:00 P.M.	*Lunch*	*Vinalhaven*
	SESSION 2: Experiences in Implementing Precision Medicine **3.5 CME, 3.5pt PA MOC**	*North Haven*
1:00 P.M.	Integration of Genomics into Clinical Pathways **Andrew Hertler, M.D., F.A.C.P. | New Century Health**	
2:00 P.M.	Implementation of the Precision Medicine Program at InterMountain Health **Lincoln Nadauld, Ph.D., M.D. | InterMountain Health**	
3:00 P.M.	Breakout Session: Implementing Cancer Somatic Testing in Community Oncology Practice **Paul Han, M.D. | Maine Medical Center Research Institute**	*Break out rooms: Penobscot Bay, Owl's Head, Spruce Head*
4:30 P.M.	*Break*	
5:00 P.M.	Reception	*Vinalhaven*
6:00 P.M.	*Dinner*	*Vinalhaven*
7:30 P.M.	*Cash Bar — JAX team available for Q&A*	*Enoteca Lounge*

Sunday April 8, 2018

8:00 A.M.	*Breakfast*	*Vinalhaven*
8:45 A.M.	Networking and Free Time	*Vinalhaven*
10:30 A.M.	*Hotel Check-out*	
11:00 A.M.	**FORUM ADJOURNED**	

Certified CME Educational Activities

MAINE CANCER GENOMICS INITIATIVE (MCGI)

The 2018 MCGI Forum will provide educational content during two in-person sessions on Saturday, April 7th.

The first session will focus on the promise of precision medicine and will feature presentations on recent scientific and clinical advancements as well as working sessions on Communicating with Patients About Cancer Somatic Testing.

The second session will feature presentations by experts in the field who have implemented precision medicine programs and a working group on Implementing Cancer Somatic Testing in Community Oncology Practice.

These sessions will offer up to 6.5 AMA PRA Category 1 Credits™ and 1.5 ABIM Medical Knowledge Points and 5.0 ABIM Practice Assessment Points. For more information, visit the event registration desk or contact us at mcgi@jax.org.

Overview

While somatic cancer panel tests are available clinically to oncologists, many questions remain on how to best integrate them into clinical practice. Major questions include when to incorporate genomic testing during the course of a patient's care to achieve maximum benefit and whether repeated testing can serve to track cancer evolution and refine treatment regimens. Addressing these questions ultimately depends on the clinician's ability to understand the genomic information being provided by tests and to efficiently extract and evaluate actionable results. The lack of education in the theory and application of cancer genomics from most clinical training programs remains a principal barrier to widespread adoption of cancer genomic testing. The Maine Cancer Genomics Initiative (MCGI) aims to overcome these barriers. The MCGI Genomic Tumor Board session series functions as an initial educational opportunity for Maine oncology clinicians with the objectives outlined below.

Learning Objectives

After attendance participants should be able to:

- Recognize the application of Precision Medicine in clinical care
- Assess the use of Precision Medicine in practice; appraise the benefits and limitations of Precision Medicine for an individual patient case.
- Effectively communicate benefits and limitations of cancer somatic tests to patients
- Identify and address barriers to effective implementation of cancer somatic testing into oncology practice in community settings

Target Audience

Maine clinicians practicing oncology, involved in cancer patient care and/or cancer research.

Claiming CME Credit

After the Forum an electronic evaluation is sent to participants who signed the in-person hard copy sheet.

CME credit is AMA PRA Category 1 Credit(s) TM and is intended for physicians. However, the MCGI Forum will offer CME credit documentation to any participant claiming it who has completed the evaluation survey. For participants who are not clinicians, it is their responsibility to determine if their licensure agency will accept the credits.

A CME documentation certificate is provided to clinicians via email after the electronic evaluation results are received.

ABIM CME MOC ACCREDITED

Accreditation and Joint Sponsorship

The 2018 MCGI Forum sessions are a certified Continuing Medical Education Activity sponsored by the Maine Medical Education Trust.

AMA Designation Statement: The Maine Medical Education Trust designates this live activity for a maximum of 6.5 AMA PRA Category 1 Credit(s) TM. Physicians should only claim credit commensurate with the extent of their participation in the activity.

CCMEA Accreditation Statement: Maine Medical Education Trust is accredited by the Maine Medical Association's Committee on Continuing Medical Education to provide continuing medical education (CME) to practicing physicians.

Joint Sponsorship: This activity has been planned and implemented in accordance with the Essentials and Standard of the Maine Medical Associate Committee on Continuing Medical Education and Accreditation through the partnership of Maine Medical Education Trust and The Jackson Laboratory.

The Maine Medical Education Trust is accredited by the Maine Medical Association to provide CME activities for physicians.

ABIM Recognition Statement: Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 1.5 Medical Knowledge MOC points and 5.0 Practice Assessment MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

MCGI Forum Support

There is no commercial support for the MCGI Forum or its educational activities. The Maine Cancer Genomics Initiative (MCGI) is a program of The Jackson Laboratory (JAX) funded through a generous grant by the Harold Alfond® Foundation.

The Jackson Laboratory (www.jax.org) is an independent, nonprofit biomedical research institution with more than 1,800 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.

Founded in 1950, Harold Alfond® Foundation furthers the philanthropic legacy of Harold Alfond, the founder of Dexter Shoe Company and a longtime supporter of Maine communities in which he and his family worked and resided. Harold Alfond awarded matching challenge grants to organizations to build community partnerships and to inspire and leverage additional giving by others. He ensured his philanthropy would live on by committing nearly all of his wealth to the Foundation, which continues to support charitable causes in the State of Maine.

American Disabilities Act (ADA)

Services for the disabled. If special arrangements are required for an individual with a disability to attend this course, please contact JAX's Jennifer Bourne at 207-288-6113 or jennifer.bourne@jax.org.

Forum Presenters

MAINE CANCER GENOMICS INITIATIVE (MCGI)

Andrey Antov, Ph.D., M.B.A.

Dr. Antov is the Program Director for MCGI. His healthcare professional experience includes basic research, medical device contracting and pharmaceutical. He has held a number of different roles from administration to consulting. Andrey holds a Ph.D. in immunobiology and a M.B.A. in marketing and strategy from Yale University as well as a M.Sc. in biochemistry and a M.Sc. in ecology from The Sofia University in Bulgaria.

Jeff Chuang, Ph.D.

Jeffrey Chuang is an Associate Professor at The Jackson Laboratory for Genomic Medicine specializing in computational analysis of large-scale cancer genomics datasets, evolution of intratumoral cell populations and mechanisms of resistance to therapy. He has been the recipient of multiple grants from the National Cancer Institute, National Human Genome Research Institute and National Science Foundation, among others, including a current role as Principal Investigator of the Data Commons and Coordination Center for the NCI Patient Derived Xenografts Development and Trial Centers Research Network. Prior to joining JAX, Dr. Chuang was an Assistant Professor in the Biology Department at Boston College. Dr. Chuang received his B.A. in Chemistry and Physics from Harvard College in 1996 and his Ph.D. in theoretical physics from MIT in 2001, then conducted his postdoctoral training in computational biology at the University of California, San Francisco.

Paul Han, M.D., M.A., M.P.H.

Dr. Han leads activities related to decision support and outcomes assessment for MCGI.

Dr. Han is the Director of CORE, a behavioral and health services researcher, and a board-certified general internist and palliative care physician. He received a M.D. from the New York University School of Medicine, and a M.A. in Bioethics and a M.P.H. from the University of Pittsburgh. He completed Internal Medicine residency training at UCLA, and a fellowship in cancer prevention and control at the National Cancer Institute (NCI).

Dr. Han's research program focuses on understanding and improving the communication and management of uncertainty in health care, and his work bridges the disciplines of health services and behavioral research. His specific research projects focus on risk communication, shared decision making and predictive modeling, and examine various clinical problems in cancer care, genomic medicine and palliative and end-of-life care. His clinical activity is in palliative medicine, and he is an attending physician at the Hospice of Southern Maine. He currently serves as the Principal Investigator of the Maine LungCAPS Initiative, a statewide lung cancer prevention and screening program primarily funded by the Bristol-Myers Squibb Foundation and the Maine Cancer Foundation.

Dr. Han is actively involved in initiatives to promote shared decision making and to teach risk communication skills to medical students and physicians. He is currently a member of the Editorial Board of Medical Decision Making, and the External Advisory Board of the NCI Cancer Research Network.

Andrew Hertler, M.D., F.A.C.P.

Dr. Hertler, as the Chief Medical Officer of New Century Health, is responsible for the advancement of the company's clinical quality initiatives, value-based strategies and utilization management policies and operations. A board certified oncologist who left clinical practice in 2014, he is a nationally recognized leader in oncology clinical practice. Dr. Hertler is a member of several American Society of Clinical Oncology committees, including the Clinical Practice, Quality of Care and Payment Reform Committees.

Prior to joining the New Century Health in 2014, Dr. Hertler was the Administrative Medical Director for Physician Practices at Maine General Medical Center and the Medical Director of the Harold Alfond Center for Cancer Care in Augusta, ME. He is a past president of the Northern New England Clinical Oncology Society. Earlier in his career, Dr. Hertler was Assistant Professor of Medicine in Hematology/Oncology at the Louisiana State University Medical School.

Edison T. Liu, M.D.

Dr. Liu is president and CEO of The Jackson Laboratory. Previously, he was the founding executive director of the Genome Institute of Singapore (2001–2011), and was the president of the Human Genome Organization (HUGO) from 2007 to 2013. Between 1997 and 2001, he was the scientific director of the National Cancer Institute's Division of Clinical Sciences in Bethesda, MD, where he was in charge of the intramural clinical translational science programs. From 1987 to 1996, Dr. Liu was a faculty member at the University of North Carolina at Chapel Hill, where he was the director of the UNC Lineberger Comprehensive Cancer Center's Specialized Program of Research Excellence in Breast Cancer; the director of the Laboratory of Molecular Epidemiology at UNC's School of Public Health; chief of Medical Genetics; and the chair of the Correlative Science Committee of the national cooperative clinical trials group, CALGB. Dr. Liu is an international expert in cancer biology, genomics, human genetics, molecular epidemiology and translational medicine. Dr. Liu's own scientific research has focused on the functional genomics of human cancers, particularly breast cancer, uncovering new oncogenes, and deciphering on a genomic scale the dynamics of gene regulation that modulate cancer biology. He has authored over 300 scientific papers and reviews, and co-authored two books. He obtained his B.S. in chemistry and psychology, and his M.D., at Stanford University. He served his internship and residency at Washington University's Barnes Hospital in St. Louis, followed by an oncology fellowship at Stanford. From 1982 to 1987 he was at the University of California, San Francisco, at the G.W. Hooper Foundation.

Lincoln Nadauld, M.D., Ph.D.

Lincoln Nadauld, Ph.D., M.D. is the Executive Director of Precision Medicine and Precision Genomics at InterMountain Healthcare, an integrated healthcare system located in the InterMountain West. Dr. Nadauld oversees the clinical implementation of genomic cancer medicine across InterMountain Healthcare's 22 hospitals and 180 physician clinics.

Dr. Nadauld completed his undergraduate education at Brigham Young University and went on to complete combined M.D./Ph.D. and clinical training at the University of Utah. He completed additional clinical training in Medical Oncology at Stanford University School of Medicine, where he also completed a postdoctoral fellowship in solid tumor genomics. While at Stanford, Dr. Nadauld received the prestigious Young Investigator Award from the American Society of Clinical Oncology, and a Career Development Award from the National Cancer Institute. He remains on the research faculty at Stanford University School of Medicine focusing on cancer genomics and personalized cancer medicine. His work has been published extensively in journals such as Nature Medicine, Journal of Clinical Oncology, and Genome Medicine. He also serves on the Board of Directors of the Gastric Cancer Foundation and regularly reviews grant applications on behalf of the Department of Defense.

In 2016, Dr. Nadauld participated in the Precision Medicine Initiative Summit and round tables at the White House with former President Barack Obama. He also attended former Vice President Joe Biden's Cancer Moonshot Summit, where the Oncology Precision Network (OPeN), spearheaded by Dr. Nadauld, was mentioned among the Vice President's remarks. OPeN is a consortium of healthcare partners working to advance data-sharing in precision medicine, including genomic information and outcomes.

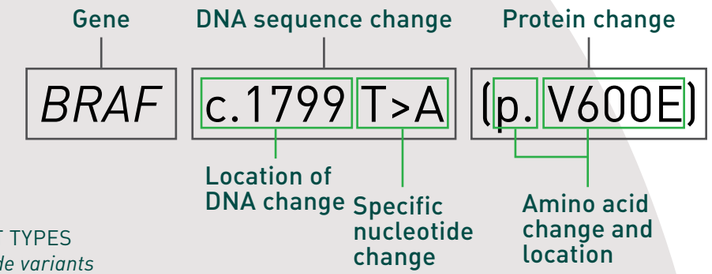
Jens Rueter, M.D.

Dr. Rueter is the Medical Director for MCGI. Dr. Rueter came to The Jackson Laboratory (JAX) in 2016 from Eastern Maine Medical Center Cancer Care, where he was the medical director for Eastern Maine Medical Center's (EMMC) Translational Oncology Program and the EMMC Biobank. He has been a hematologist/oncologist at EMMC Cancer Care since 2010, and a member of the JAX adjunct faculty since 2012. Prior to joining JAX, Dr. Rueter collaborated with several JAX investigators and technicians on developing new approaches to treating cancers while advancing translational research at EMMC.

After graduating from medical school in Berlin, Germany, Rueter completed his residency in internal medicine at Tulane University and fellowship training in hematology/oncology at the University of Pennsylvania.

Test Report Nomenclature

Laboratories use a common nomenclature system to identify variants. In this resource, the elements of that system are explained.



COMMON NOTATIONS AND ABBREVIATIONS

General	
SNV	Single nucleotide variant
CNV	Copy number variant

Location	
c.	Coding DNA reference sequence
n.	Non-coding DNA reference sequence

Functional impact	
p.	Protein change

Nucleotide change types	
>	Substitution
Del	Deletion
Dup	Duplication
Ins	Insertion
Inv	Inversion
Fs	Frame shift

VARIANT TYPES

Nucleotide variants

DNA Sequence	Nomenclature	Meaning
T C G T G T A		Reference DNA sequence
T C G C G T A	c.4T>C	SNV - Single Nucleotide Variant
T C G T A G T A	c.4_4insA	Insertion
T C G _ G T A	c.4delT	Deletion
T C G C C G _ G T A	c.4delinsCCG	Indel - insertion and deletion
T C G C G T G T A	c.4_5dupCG	Duplication

Other Variant types

Variant Type	Nomenclature	Meaning
Copy number variant	Amplification (amp)	Section of DNA repeated
	Deletion (del)	Section of DNA deleted
Rearrangement	Fusion	2 genes broken and re-attached together, which can activate oncogenes

TERMINOLOGY

Variant refers to any difference in the DNA sequence compared to a reference genome.
Variants may or may not have an impact on the function of the gene.

- Benign or likely benign variants do not have any functional consequences and are often seen commonly in the general population. You may also see these referred to as “polymorphisms.”
- Pathogenic or likely pathogenic variants impact the function of the gene in some way. Most accurately, these are referred to as “variants that impact function”. More commonly, these may be referred to as “mutations.”
- Variants of unknown significance or VUS are changes in the gene for which the impact is unknown. This may be because they are rare and there is not enough data available to be conclusive about their functional impact. Over time, VUS are likely to be re-classified as benign or pathogenic as more data are amassed.
- Copy number variation is when a section of DNA is repeated or a section of repetitious DNA is deleted.

FUNCTIONAL IMPACT OF SEQUENCE VARIANTS

Impact	Meaning	Example
Silent	Variant does not change amino acid/protein and is unlikely to affect function	CGT to CGC Arginine to Arginine
Missense	Variant changes amino acid	GTA to GAA Valine to Glutamic Acid
Nonsense	Variant changes amino acid to stop codon	TCA to TAA Serine to stop

FOR MORE INFORMATION

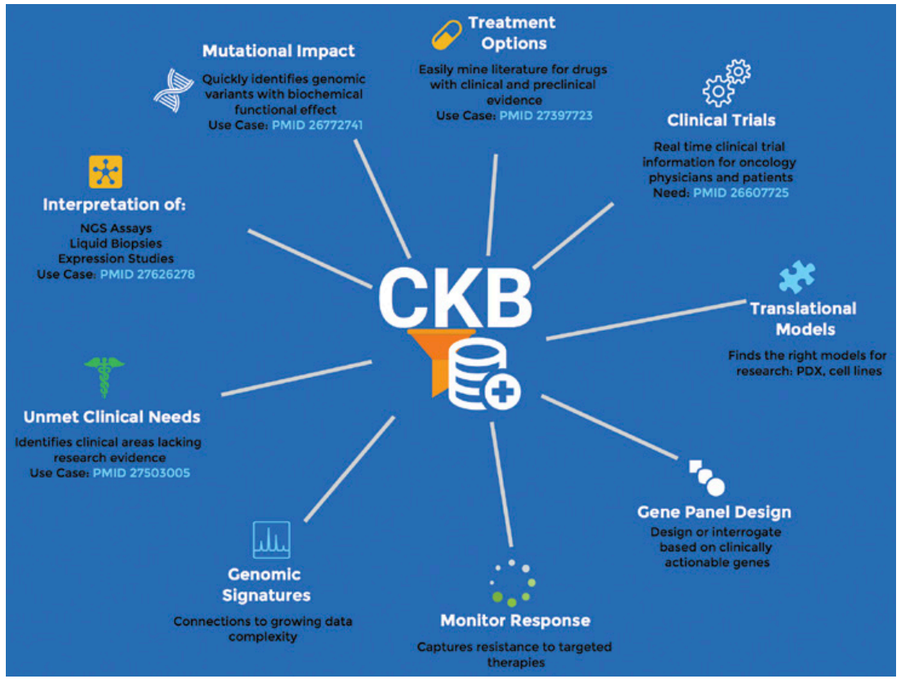
Sequence Variant Nomenclature: Recommendations for the description of sequence variants. Nomenclature authorized by Human Genome Variation Society (HGVS), Human Variome Project (HVP), and the HUman Genome Organization (HUGO).

CKB Capabilities

Promises of precision oncology have enabled progress in patient care, but with this comes the challenge of an overwhelming amount of data burying the proverbial needle in a haystack. Identifying the needle, or a potential therapeutic target, from the haystack of genomic data using traditional literature searches can be a tedious process. A knowledgebase, such as the JAX-Clinical Knowledgebase (JAX-CKB), strives to structure the available literature into a format that is easy to navigate, while maintaining the integrity of the data. The JAX-CKB is an integrated knowledgebase that contains data on genomic variants, targeted therapies, clinical trials and evidence of therapeutic efficacy in oncology. These data are curated from the published literature into the JAX-CKB on a daily basis by a team of Ph.D. scientists, to ensure the most up-to-date content possible. On top of this database sits a searchable publicly accessible interface (ckb.jax.org) that enables easy searching on genes, gene variants, therapies and tumor types, as well as advanced searching for therapeutic evidence and clinical trials. In this way, the JAX-CKB can impact healthcare in real time. A user, such as an oncologist, has access to information at their fingertips that can aid in therapeutic decision making.

The JAX-CKB makes meaningful connections between genomic variants, therapeutic efficacy, and tumor type, and supports easy retrieval of information based on those connections. For example, a given genomic variant can be connected to a therapy and response in the context of a specific tumor type, supported by manually curated efficacy evidence annotation. A user searching on a specific gene variant will find an interpretation of that variant, if available, and will also be able to navigate to the related evidence data in the JAX-CKB. This allows the user to assess the functional significance of a variant, and may provide some insight into potential therapeutic options. The JAX-CKB can function as an initial portal for somatic variant interpretation, and can complement the more extensive interpretation support provided in the setting of a genomic tumor board.

The JAX-CKB has over 20,000 users to date, spanning 107 countries, and continues to inform patient cancer care while contributing to development of technology and methodology to advance the field of oncology precision medicine. Key commercial collaborators are aiding sustainability of the JAX-CKB by leveraging machine-learning capabilities. Additionally, third-party software platforms have integrated the JAX-CKB to enable easy and scalable access for use in informing cancer patient care. The unique position of JAX, with world-renowned principal investigators, will continue to power the depth and quality of CKB, enabling the latest knowledge to flow from the front lines of cancer research to the clinician and patient.



CLINICAL KNOWLEDGEBASE (CKB)

Basic Search
Explore by Gene
Explore by Variant
Explore by DrugClass
Explore by Drug
Explore by Indication

Advanced Search
Clinical Trial Search
Evidence Search

CKB OPEN ACCESS
ckb.jax.org

CLIA Lab Briefs

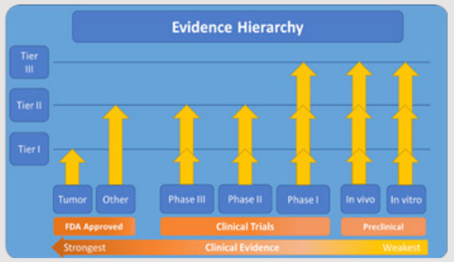
Team

Andrew Hesse, M.S., M.B. (ASCP), clinical data analytics & reporting manager
Matthew Prego, clinical genomic analyst
Greg Lewis, Pharm.D., R.Ph., clinical genomic scientist
Bridgette Sisson, clinical genomic analyst
Pavalan Selvam, M.B.B.S., clinical genomic scientist

Joint AMP/ASCO/CAP Variant Classification

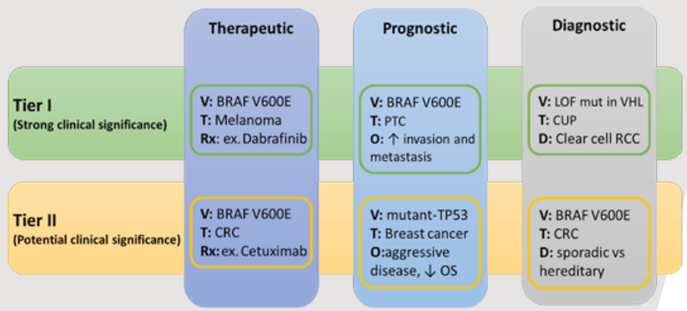
The Clinical laboratory at The Jackson Laboratory (JAX) is one of the earliest adopters of the recent 2017 joint (AMP/ASCO/CAP) guidelines on interpretation and reporting of somatic variants in cancer[1]. The classification system is broken down into 4 tiers (tier I, II, III and IV; figure 1) containing 3 subclasses (figure 2): Therapeutic (Rx), prognostic (Px) and diagnostic (Dx). Variants in tier I (strong clinical significance) serve as predictive markers for response to FDA-approved drugs indicated for the patient or recommended by guidelines for testing as Px or Dx markers of the patient tumor. Variants in tier II (potential clinical significance) serve as markers for either off-label use of FDA-approved drugs or investigational drugs with clinical trial evidence supporting use in the patient tumor or serve as eligibility criteria for inclusion in clinical trials. Tier III (unknown clinical significance) are variants that do not meet the criteria for inclusion in tiers I, II and IV, or have evidence with conflicting interpretations. Tier IV are considered benign variants and not included in reports as standard protocol. These variants are observed at polymorphic frequencies in large cohorts or have direct evidence demonstrating lack of disease involvement.

Figure 1: Stratification of evidence in variant classification



Overview of the types of evidence and their contribution to the different variant classes. Preclinical can enrich support for a variant or justify class upgrade, but will not alone reach Tier II. FDA drug for patient/tumor profile is default Tier I. Tier IV variants (not displayed) are benign/likely benign and not included on the final report.

Figure 2: Examples of Tier I/II classification



Legend: V= variant, T= tumor type, Rx= Drug, O= associated Px outcome, D= associated Dx outcome, ↑/↓=increase/decrease

[1]Li MM, et al. Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists. J Mol Diagn 2017;19-23.

Overview of Gene and Variant Interpretation

All ActionSeq Plus reports contain gene and variant summaries based on interpretive findings. Gene descriptions cover fundamental clinical genetic information such as the encoded protein and its primary function, disease mechanism, common variant types, common tumors associated with aberrant forms of the gene and a brief overview of the therapeutic landscape. Similarly, variant descriptions include information such as the impacted protein domain, molecular function, pathogenic mechanism and tumors known to harbor the specific aberration (Figure 1). Evidence supporting the role of these genetic findings in cancer are collected from peer-reviewed literature, public databases and a variety of computational tools to assess clinical significance. Due to the rapid pace of oncology research, comprehensive re-assessment of variants is conducted on a six-month cycle to ensure the most accurate and current information is provided in a clinical report.

Gene Level	
Molecular	Gene function and role tumorigenesis
Genetic	Common mutations and cancer signaling pathway
Pathology	Known cancer types gene effects
Clinical	Drug landscape

Variant Level	
Molecular	Mechamism of oncology
Genetic	Type of mutation as well as where it is located in the genome
Pathology	Known cancer associations
Clinical	Drug landscape

Overview of Clinical Interpretation

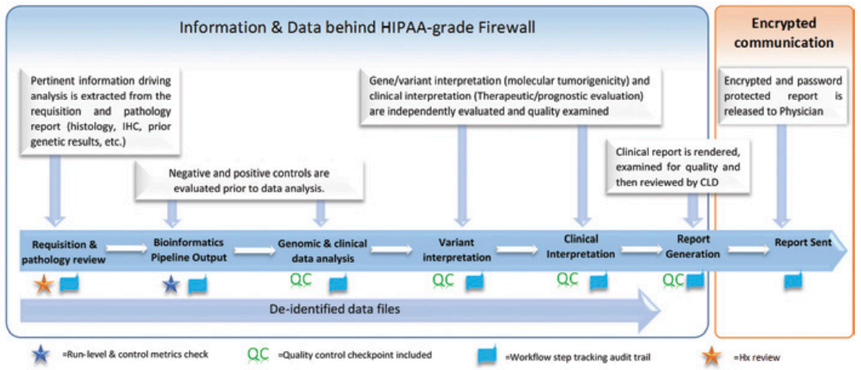
All ActionSeq Plus reports contain summaries for the targeted drugs included based on interpretive findings. Both approved and investigational drug descriptions cover fundamental pharmaceutical information such as the USAN generic name, brand name, drug class and mechanism of action in addition to an overview of the clinical evidence associating the drug with the genomic alteration. FDA approved therapies also contain the current approval status and prescribing indications. Additionally, *www.clinicaltrials.gov* is reviewed and targeted clinical trials that potentially provide therapeutic avenues for the patient based on their genomic profile and pathology report are also included. Evidence supporting the role of these therapeutic findings in cancer are collected from *www.fda.gov*, NCCN clinical practice guidelines, peer-reviewed literature, public databases and JAX-CKB. Based on this information, variants with molecular classifications are clinically classified according to the joint AMP/ASCO/CAP variant interpretation guidelines[1].

FDA-Approved	
Molecular	Mechanism of action
Genetic	Targeted aberrations and resistance by other detected variants
Pathology	Evidence in cancer types, gene-drug response outcomes
Clinical	Approved indication(s), response to gene(s) for other indications

Variant Level	
Molecular	Known mechanism of action
Genetic	Targeted aberrations and resistance
Pathology	Evidence in cancer types, gene-drug response outcomes
Clinical	Putative indication(s), trials

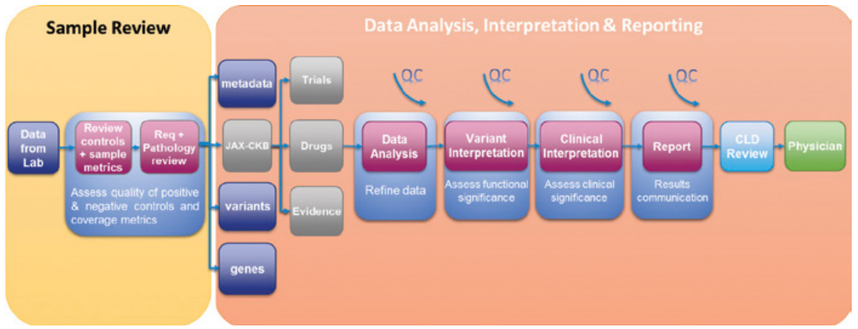
Overview of Analysis & Reporting Quality Processes

Quality Control (QC) and chain of custody are the hallmarks of clinically accredited laboratories such as the CLIA/CAP-accredited genomic testing lab at JAX. For Analysis & Reporting (A&R), we have taken a Quality by Design (QbD) approach integrating four primary QC steps with dynamic dataflow that affords us the flexibility to adapt to the case-by-case complexity of genomic testing in oncology. Patient data entering A&R has unique de-identified sample IDs generated by the LIMS system that are used to establish traceability from start to finish, tracking who worked on the samples, when they were worked on, the client and the assays performed. Samples are initially assessed for overall performance metrics and experimental controls, followed by review of the requisition, pathology report or other available medical history that will help focus analysis. Independent results QC is performed post data analysis, molecular/functional interpretation, clinical interpretation and report generation before going to the Clinical Laboratory Director for final case review and approval. All variants are re-assessed for functional and clinical significance in six-month intervals to ensure information remains current in the quickly evolving genomics field. This all happens behind the JAX clinical firewall exceeding HIPAA security standards. A clinical report only leaves the JAX firewall when sent to the ordering physician, and it does so as an encrypted and password protected PDF via DocuSign.



Requisition and Pathology Report Review

Over the past few months, A&R CLIA briefs have touched on the quality control processes, variant classification system, as well as the molecular and clinical variant interpretation methods used to transform DNA sequencing data into the clinical test reports issued to physicians (figure 1). Another important component of this process is initial review of the medical history information gathered from the requisition, pathology report and other test result findings, which can fine tune the relevance of clinical trials as well as the evidence for variants and therapies. Parameters such as hormone receptor status, previously identified genetic mutations, or other laboratory results that narrow focus of the somatic test results facilitates removal of non-eligible trials, inclusion/exclusion of known resistance mechanisms and higher specificity evidence to associate with detected variants during analysis and interpretation. We are happy to provide re-analysis of data upon request or further review variants with additional information that may influence variant classification.



Information about test processing status is available by contacting Clinical Lab Customer Service, jaxmoleculardx@jax.org. The customer service direct line is 860-837-2162. If you have any additional questions related to technical or scientific aspects of the test, please do not hesitate to reach out to our Clinical Laboratory Director, Honey Reddi, Ph.D., FACMG at (860) 837-2062.

Genomic Tumor Board

The MCGI Genomic Tumor Board Sessions

The MCGI Genomic Tumor Board (MCGI GTB) sessions are a series of meetings coordinated as part of the Maine Cancer Genomics Initiative. During a genomic tumor board meeting, report results from clinical genomic tumor testing are discussed with a panel of expert external advisors, oncologists and pathologists from the MCGI network — clinical trial and genomic testing experts. The goal of the sessions is to provide interpretation support for treating clinicians and to allow the assembled community of M.D.s to discuss potential treatment options for the patient. MCGI GTB addresses a barrier to wider adoption of cancer genomic testing in clinical care — the interpretation of clinical genomic test results. The report includes a significant amount of curated data to give a clinician the highest amount of information to aid in treatment decisions. However, the process of interpreting this information and translating it into clinical care can be time consuming. The MCGI GTB is designed to facilitate this process. Clinicians attending the MCGI genomic tumor board sessions benefit from the input of a number of experts in the field in a discussion moderated by MCGI Medical Director Jens Rueter, M.D. Our genomic tumor board advisors have extensive experience in using clinical genomic tumor testing results to guide patient treatment. After the conclusion of each meeting, minutes for the session detailing the discussion and potential treatment options are distributed to attendees.

GTB Session Content

The MCGI GTB meetings feature the presentation of one or more case-vignettes, drawn from real-world patients who have consented to participate in the MCGI study. All review of clinical information will be done in a coded-manner. Protected health information (PHI) will not be disclosed in the GTB meetings.

Information reviewed will include the patient's diagnosis, pertinent history of illness, previous treatment approaches and results from the MCGI study-related genomic cancer test. At the discretion of the presenter, pathology findings and other information about the case pertinent to clinical decision making may also be discussed.

Commentary and discussion will center on genomic variant interpretation, pathology, oncology and community knowledge of similar cases. A treatment recommendation will be recorded after the discussion for each case is reviewed.

GTB Session Format

Meeting attendance is offered in person at select MCGI study sites on a rotating basis and sessions are open virtually via conference call and presentation content sharing. Interested clinicians can attend in person at a study site, by teleconference or video-teleconference, allowing providers from across the State of Maine to access this educational activity without need for travel.

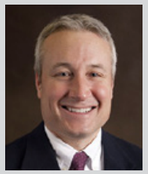
Genomic Tumor Board Sessions, to date, have attracted a large number of participants from across the Maine Oncology Community. AMA PRA Category 1 Credits™ are offered for participation in GTB sessions. Reach out to us at mcgi@jax.org for more information and to be added to the invitation list.

Steering Committee

MAINE CANCER GENOMICS INITIATIVE (MCGI)

Philip L. Brooks, M.D.

Dr. Brooks practices at Eastern Maine Medical Center (EMMC) and oversees their clinics at the Mt. Desert Island Hospital, the Maine Coast Memorial Hospital, and the Blue Hill Memorial Hospital. He is board certified in internal medicine, hematology and medical oncology caring for patients in all areas of medical oncology, hematologic oncology and benign hematology. He received his M.D. from the University of Pennsylvania School of Medicine before completing his medical residency at the University of Pennsylvania-Presbyterian Medical Center. He completed a three-year fellowship in hematology/oncology at Dartmouth-Hitchcock Medical Center. Dr. Brooks spent time in China as Senior Vice President of Medical Affairs and Chief of Oncology Development for United Family Healthcare.



Robert Christman, M.D.

Dr. Christman is the Maine Medical Center (MMC) Pathology Department Chief and Medical Director of MMC hematology, NorDx Flow Cytometry and Molecular Pathology Laboratories. He holds board certification from the American Board of Pathology in anatomic pathology, clinical pathology and hematology. Dr. Christman received his M.D. from Temple University School of Medicine, where he also served his residency and held a fellowship position.

Elizabeth (Betsy) Connelly, D.O.

Dr. Connelly practices medical oncology and hematology at Waldo County General Hospital and Pen Bay Medical Center. She is board certified in medical oncology, hematology and internal medicine. Dr. Connelly is a member in the American Society of Clinical Oncology and is on active staff at Waldo County and Pen Bay Medical Center. She received her D.O. from Texas College of Osteopathic Medicine followed by a residency at Akron General Medical Center in internal medicine and a fellowship with the Cleveland Clinic Foundation in medical oncology/hematology.

Christopher Darus, M.D.

Dr. Darus practices gynecologic oncology at Maine Medical Center. He holds board certification from the American Board of Obstetrics and Gynecology and specializes in gynecologic oncology. Dr. Darus received his M.D. from Wright State University School of Medicine, followed by a residency at University of Colorado Health Sciences Center and a fellowship at University of Virginia Medical Center.

Nicholette Erickson, M.D.

Dr. Erickson practices at Hematology-Oncology Associates in Lewiston, ME. She is board certified in Hematology and Medical Oncology. She received her M.D. from Medical College of Virginia followed by a residency in Internal Medicine and a Fellowship with the University of Virginia Health Sciences Center in Hematology-Oncology.

Peter Georges, M.D.

Dr. Georges practices Oncology at York Hospital in Southern Maine. He holds board certification in internal medicine, hematology and medical oncology. Dr. Georges received his M.D. from Georges University School of Medicine in Grenada, West Indies followed by an internship and residency at University of Massachusetts. He completed his fellowship in hematology/oncology at M.D. Anderson Cooper Cancer Center, Cooper Medical School of Rowan University.

Antoine Harb, M.D.

Dr. Harb practices oncology at Eastern Maine Medical Center (EMMC) and is affiliated with Blue Hill Memorial Hospital. He is board certified in hematology, internal medicine and medical oncology. He takes a special interest in thoracic, head and neck, and neuro-oncology. Dr. Harb received his M.D. from Saint Joseph University, where he also served his residency in internal medicine. Later Dr. Harb did an additional residency at University at Buffalo followed by a fellowship in hematology/oncology at UM.D.NJ (University of Medicine and Dentistry of New Jersey)-Cooper Medical Center.

Roger C. Inhorn, M.D., Ph.D.

Roger Inhorn is the Chief of Oncology at Mercy Hospital in Portland, Maine. He is a graduate of the M.D./Ph.D. program at Washington University Medical School. He completed his internal medicine residency at Brigham and Women's Hospital followed by a medical oncology fellowship at the Dana-Farber Cancer Institute. Dr. Inhorn practiced in St. Louis for seven years, where he was Associate Director of Hematology/Oncology at St. John's Mercy Medical Center, prior to relocating to Maine. He has a special interest in breast cancer and clinical trials.

Rachit Kumar, M.D.

Dr. Kumar is a medical oncologist and hematologist who sees patients at the Harold Alfond Center for Cancer Care and the Alfond Center for Health in Augusta. A member of MaineGeneral Medical Center's active staff, he joined the cancer staff in July 2017 after completing a hematology/oncology fellowship at Georgetown University/MedStar Washington Hospital Center in Washington, D.C. He received his medical degree from Maulana Azad Medical College, New Delhi, India and then did his internal medicine residency and chief residency at Georgetown University/MedStar Washington Hospital Center. His interests include targeted therapies and immunotherapy.

Mayur K. Movalia, M.D.

Dr. Movalia is a Pathologist with Dahl-Chase Pathology Associates in Bangor, ME. He holds board certifications from the American Board of Pathology in anatomic and clinical pathology and hematopathology. Dr. Movalia received his M.D. from Flinders University School of Medicine followed by an internship in internal medicine and a pathology residency at University of Hawaii, as well as a hematopathology fellowship at Hartford Hospital.

G. Richard Polkinghorn, M.D.

Dr. Polkinghorn was a practicing oncologist at Maine Medical Center and Mid Coast Hospital for 14 years prior to coming to Maine General Medical Center. His professional interests include breast cancer and lung cancer involving novel and targeted therapies. Dr. Polkinghorn received his M.D. from Case Western Reserve University followed by an internship and residency in internal medicine at UCLA Medical Center in Los Angeles, CA, and a fellowship in medical oncology at Harbor UCLA Medical Center in Torrance, CA. He earned a M.A. in Education and taught high school science, music and sports for six years prior to entering medical school.

Nadia Rajack, M.D.

Dr. Rajack is the Medical Director at the Jefferson Cary Cancer Center. She takes a special interest in quality improvement initiatives with the goal of delivering high quality care in a rural oncology practice setting. Dr. Rajack received her undergraduate M.B.B.S. degree from the University of the West Indies. She went on to pursue postgraduate training at SUNY Downstate Health Science Center in Brooklyn, NY. She completed her residency in internal medicine, followed by a fellowship in sickle cell anemia and a fellowship in hematology and oncology. Dr. Rajack is board certified in internal medicine, hematology and medical oncology.

Karen Rasmussen, Ph.D.

Dr. Rasmussen is Director of Molecular Genetics at Spectrum Medical Group. She has extensive experience in clinical molecular genetics: development and interpretation of molecular genetic assays, including next-generation sequencing and gene expression profiling. Dr. Rasmussen has provided cancer genetic counseling in the community oncology setting. She also has experience in tumor tissue banking for research and has worked in cancer molecular genetic research, primarily identifying mutational or gene expression profiles of tumors for prognosis or prediction of response to therapy. Dr. Rasmussen received her Ph.D. from University of New Hampshire followed by a fellowship in clinical molecular genetics at the University of North Carolina School of Medicine.

Scot Remick, M.D.

Dr. Remick is Physician Leader of Oncology at Maine Medical Center Cancer Institute and Maine Health, where he specializes in internal medicine and oncology. He is board certified in internal medicine with a sub specialty of oncology. Dr. Remick received his M.D. from New York Medical College followed by a residency at Johns Hopkins Baltimore City Hospital and fellowship at University of Wisconsin Hospitals & Clinics.

Peter Rubin, M.D.

Dr. Rubin practices oncology at SMHC Cancer Care Center and is Medical Director. He is board certified in hematology and medical oncology. Dr. Rubin received his M.D. from University of Calgary followed by residencies at University of Calgary, University of Western Ontario and University of Western Ontario-Schulich School of Medicine & Dentistry. He also held a fellowship at Duke University Medical Center.

Sarah Sinclair, D.O.

Dr. Sinclair practices oncology at Eastern Maine Medical Center (EMMC) Cancer Care. She is board certified in internal medicine and medical oncology. Her interests include breast cancer, clinical research, and general oncology. Dr. Sinclair received her D.O. from University of New England College of Osteopathic Medicine followed by a residency at University of Connecticut School of Medicine in internal medicine, and a fellowship with the National Cancer Institute in hematology/oncology.

Marek Skacel, M.D.

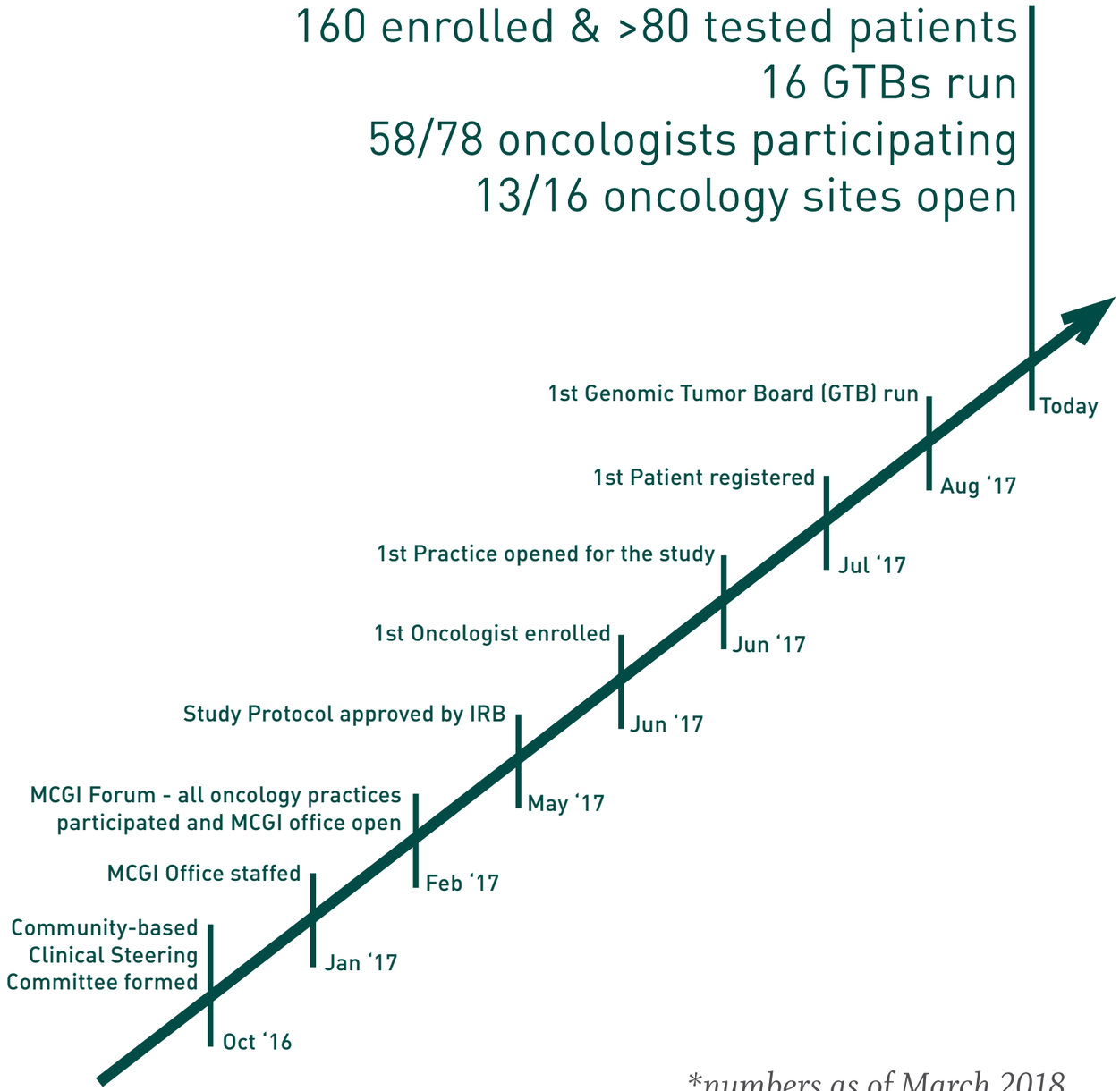
Dr. Skacel is a Pathologist at Dahl-Chase Pathology Associates in Bangor, ME. He holds board certifications from the American Board of Pathology in anatomic and clinical pathology and hematopathology. He takes a special interest in the areas of gastrointestinal pathology, genitourinary pathology, soft tissue pathology, hematopathology, and molecular pathology. Dr. Skacel received his M.D. followed by an internship at Palacky University in Olomouc, Czech Republic. Subsequently he completed residency in anatomic and clinical pathology at The Cleveland Clinic Foundation followed by fellowships in gastrointestinal, genitourinary & soft tissue pathology, molecular pathology research, hematopathology, and surgical pathology.

Christian Thomas, M.D.

Dr. Thomas joined New England Cancer Specialists as a physician and the Director of Clinical Research in 2012. His clinical focus is on thoracic cancers (lung cancer, esophageal cancer) as well as GU cancers (prostate, testicular, bladder and kidney cancers). He also serves as an advisor to the American Society of Clinical Oncology, the Northern New England Clinical Oncology Society and CMS/Medicare. Dr. Thomas completed his medical school training in Frankfurt, Germany and an internal medicine residency and hematology/oncology fellowship at Columbia University in New York City.

MCGI Timeline

160 enrolled & >80 tested patients
16 GTBs run
58/78 oncologists participating
13/16 oncology sites open



**numbers as of March 2018*

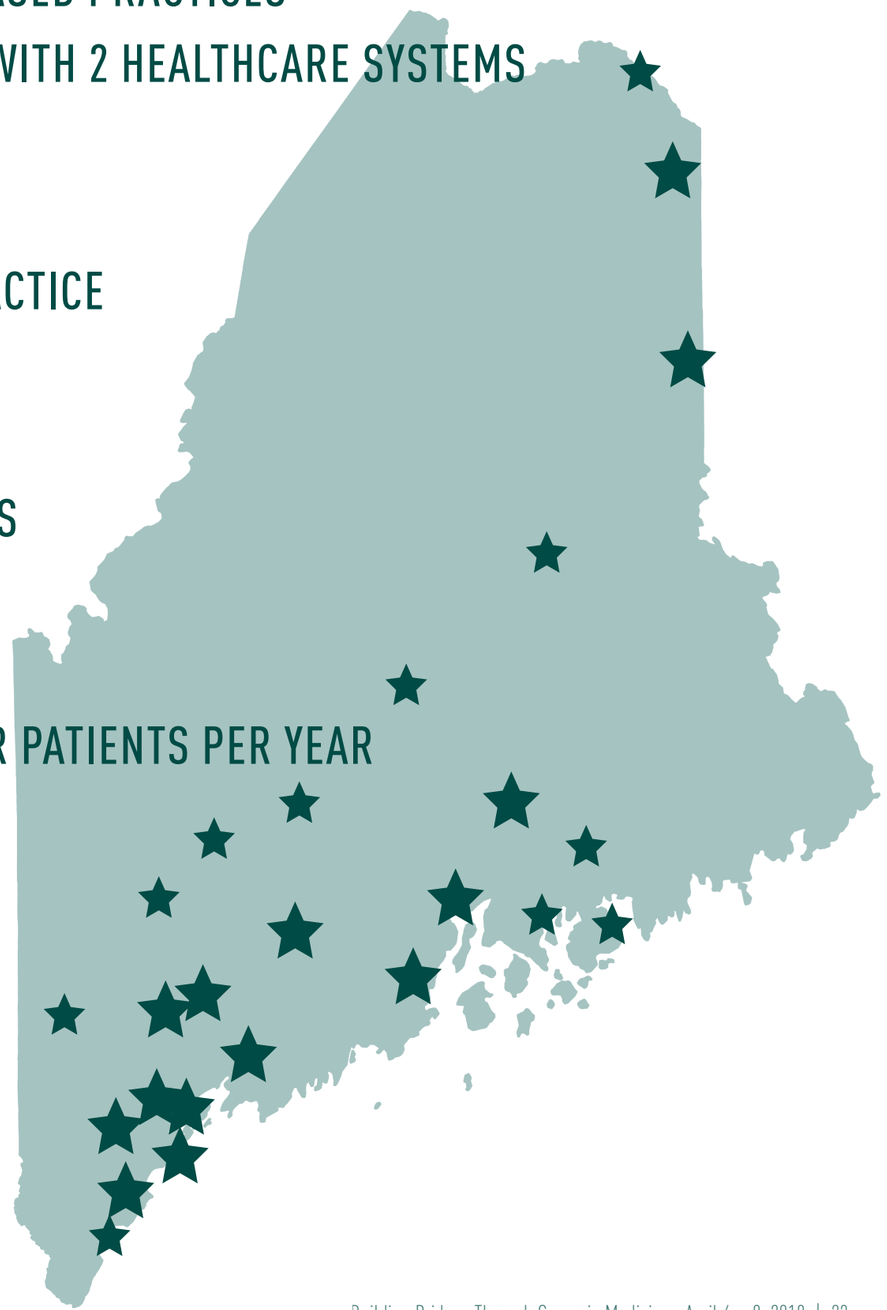
MCGI Network

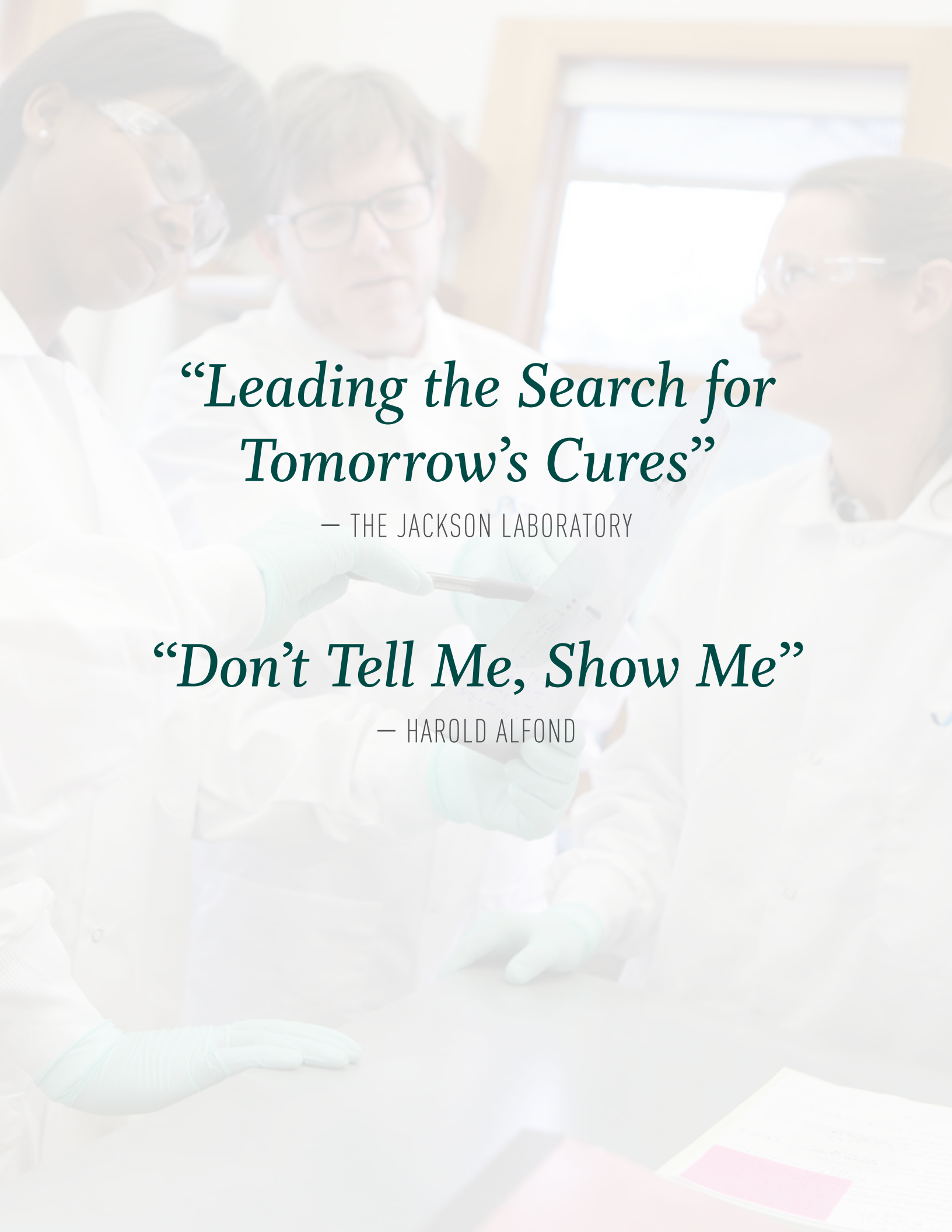
16
HOSPITAL-BASED PRACTICES
AFFILIATED WITH 2 HEALTHCARE SYSTEMS

1
PRIVATE PRACTICE

78
ONCOLOGISTS

~9000
NEW CANCER PATIENTS PER YEAR





“Leading the Search for Tomorrow’s Cures”

— THE JACKSON LABORATORY

“Don’t Tell Me, Show Me”

— HAROLD ALFOND