WHITE PAPER

Accelerating Clinical Genomics to Transform Cancer Care

What will it take to make genome sequencing part of everyday cancer care? People-centered research from Intel identifies roadblocks and suggests remedies.

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Introduction

If you're a cancer patient, genomic sequencing may be able to help your clinical team find treatments that will provide the best outcomes with the fewest side effects.

Yet today, this powerful approach is underused. Although genomic testing is available to patients at academic oncology centers and community oncology practices, it has not yet achieved widespread use in cancer care. When it is employed, is most often used to test only a small subset of your DNA (a single marker or a panel of select genes of interest) rather than the whole genome or whole exome (the subset of the genome that affect crucial protein synthesis).

Whole exome and whole genome sequencing are essential to seeing the full picture of molecular factors that may be driving an individual's cancer. This is because gene variants—not necessarily the location or type of cancer—may be the most important considerations for treatment options. Next-generation sequencing (NGS) approaches are also critical to building our understanding of the exciting new world of precision medicine. As more genes are sequenced and analyzed, scientists and researchers gain insights that can help them develop new cancer treatments and see where existing treatments may have breakthrough potential for other cancers.

What issues are limiting the full, appropriate use of genomic testing for cancer care, including NGS? What can be done to address these issues? As the cost of genome sequencing continues to fall and the number of gene-targeted therapies grows, these questions become increasingly important.

Intel's ethnographic researchers worked with physicians and patients in the United States (US) and the People's Republic of China (PRC) to understand attitudes and issues that act as barriers to widespread genomic testing. This work identified several factors that feed a "cycle of inaction" and suggests ways to address them.

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Entering a New Era: All in One Day Precision Medicine

The human genome was first sequenced in 2003 at an estimated cost of USD 2.7 billion in 1991 dollars.[1] Today, the price tag for sequencing a whole human genome is under USD 1,000 and continues to decline.

Affordable, next-generation sequencing, backed by powerful health analytics, is poised to usher in a transformative era of precision medicine. Performed early in the diagnostic process and combined with other elements of precision medicine, NGS can be a valuable part of treatment planning. Instead of one-size-fits-all treatments based on the site of the cancer, in a growing number of cases oncologists can prescribe treatments that are precisely targeted to the genetic abnormality while leaving healthy cells intact.

If a treatment fails or a cancer recurs, NGS may help clinical teams understand what's causing the recurrence and strategize an effective response. NGS data can also be used to route patients to clinical trials where they are most likely to benefit and to detect drug resistance. As more patients have their DNA sequenced, research scientists are in a better position to develop new treatments and discover areas where existing treatments show promise.

"Median years of survival for patient who receive target therapies can reach three years, but median years of survival for those who did not receive target therapies is just about one year."
- Oncologist, PRC

These changes can help increase survival rates and reduce suffering and anxiety for patients and their families. They may also offer economic benefits by getting patients back to their normal lives faster, reducing unnecessary procedures and treatments, and enabling healthcare systems to operate more efficiently.

The benefits of NGS extend well beyond cancer care. Thousands of rare conditions, along with diseases ranging from Alzheimer's to the Zika virus, have molecular elements that may prove crucial to efforts to prevent, diagnose, and treat them.

Intel has a vision of enabling cancer patients to have their tumor DNA sequenced and receive precision treatment plans based on their unique biomolecular profile, all within 24 hours. We call this All in One Day, and are centering our health and life sciences activities on achieving it. We are driving technology innovation on many fronts and collaborating with health, life science, government, and technology leaders to make All in One Day a reality, and we believe the vision is achievable by 2020.

Human-Centered Research for All in One Day

Ethnographic research is a vital part of All in One Day. These people-focused studies, conducted by highly skilled social science researchers, bring a human face to Intel's technical innovations and collaborations. By understanding the day-to-day reality of the intended user community, Intel and other organizations in our innovation ecosystem are better able to meet user needs, speed technology adoption, and ensure that next-generation technology solutions deliver their full benefits.

Intel's ethnographic work to support All in One Day is embodied by the acronym *ENACT: Exploring Novel Approaches to Care Transformation*. This paper discusses ENACT research on scaling precision medicine for cancer care in

the PRC and the US, with an emphasis on patient and clinician experiences.

Intel researchers in the US conducted ethnographic interviews with 20 oncologists: 12 who practice in community settings and 8 in academic settings. Based on the interviews, the ethnographers developed online surveys that were administered to 50 oncologists: 70 percent from community practices, 24 percent in academic settings, and 6 percent military. The ethnographers explored the attitudes and experiences of patients via interviews with 25 cancer patients. Patients varied in age from 30-70, and had been diagnosed with ovarian, breast, prostate, and colorectal cancers and lymphoma. Patient interviews were conducted by telephone. Interviews with oncologists were conducted in hospital/clinics settings, as well as by phone.

ENACT ethnographers conducted parallel research in China, where since early 2015 the National Health and Family Planning Commission (NHFPC, formerly called the Ministry of Health) has approved and recruited 21 hospitals and independent clinical test labs (ICTLs) in six provinces into the pilot clinical programs of applying NGS in cancer diagnostics and treatment. Precision medicine is expected to be a key element in the PRC's next five-year plan for science and technology development, and many hospitals are likely to expand their use of NGS sequencing.

ENACT ethnographers in China conducted contextual interviews with 35 individuals, including oncologists, patients, pathologists, independent clinical test labs or sequencing service providers, and hospital CEOs/CIOs.

Institutional Barriers: System-Level Issues Feed a Cycle of Inaction

Oncologists believe genomic testing is the wave of the future, and say its use is growing. However, they believe a variety of issues are slowing the broad use of NGS testing. And, although funding mechanisms and access to cancer care differs significantly between the PRC and the US, oncologists in both countries identify very similar roadblocks.

These issues include:

- High cost and lack of payment coverage.
- Lack of targeted therapies or other actionable options.
- NGS not defined as standard of care.
- Time needed to wait for results.

PRC oncologists also identified:

- Lack of standard guidelines such as the National Comprehensive Cancer Network (NCCN) on when to apply NGS rather than single-gene and small-panel testing.
- Methods for collecting genetic profiles of patients vary in technologies, sensitivity, prices, and accuracy.
- Availability of tumor samples.

The result of these factors is a cycle of inaction. *(See Figure 1, pg 4)* Physicians are reluctant to order tests unless they are confident the results will contribute to an actionable outcome—ideally a clear indication for an accepted treatment that will be covered by insurance or other funding. This is especially the case if the test is relatively expensive, is not covered by insurance or other funding mechanisms, or is not considered part of the standard of care at the provider's institution or practice.

Use of single-marker and panel tests has grown and become standard of care for only a very limited number of cancers. Routinely testing all patients and using NGS (whole exome or whole genome testing) has not. This means that people who may benefit from new treatments or clinical trial opportunities based on their cancer's molecular variants will not have that option available to them.

"For me, it's whether it's gonna affect a treatment decision. If it's not really going to impact the treatment decision, then I wouldn't do any testing."
- Oncologist, US

Why isn't genomic testing—particularly NGS testing—considered standard of care? In medicine, as in many other fields, innovations can take a decade or longer to become standard practice. Analysis published in the Journal of the Royal Society of Medicine identified a 17-year lag in translating medical research into practice.[2] During this lag-time, payers are reluctant to cover the costs of tests until they have clear evidence of the tests' benefit. But since oncologists aren't ordering the tests, the data to build a case for genomic testing as part of an evidence-based standard of care isn't being accumulated. And because genomic testing—in particular whole exome and whole genome testing-- is not standard of care for most cancers, payers feel justified in not covering it. It's a vicious circle.

The result is today's trial-and-error approach to cancer care. For many types of cancer, clinicians do not consider genomic testing at all, and patients receive one-size-fits-all, non-tailored treatments. If these patients receive any genome analysis, it may be only after they've failed one or more rounds of "standard" treatment. For a few types of cancer (e.g., lung, breast, and prostate), clinicians order single-marker or limited-panel tests that allow for yes/no decisions about specific treatments.

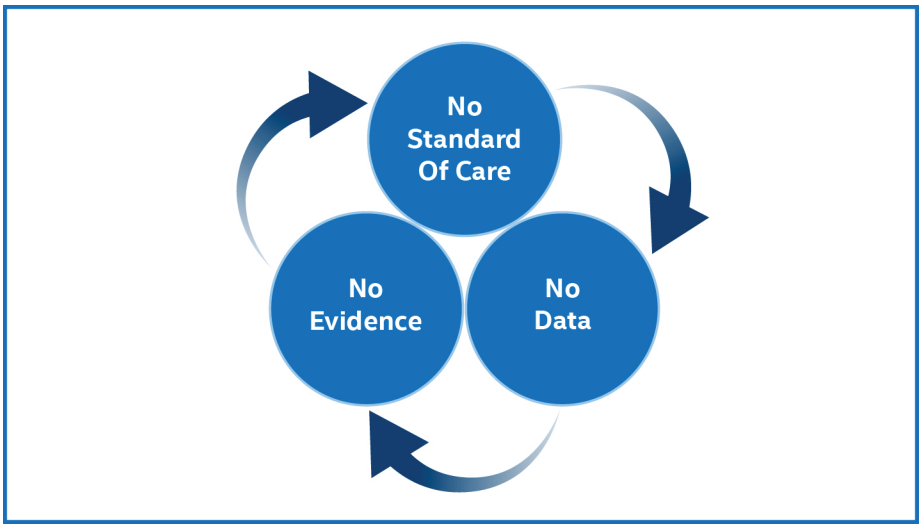

Figure 1. The Cycle of Inaction

Individual and Practice-Level Barriers

In addition to system-level issues, Intel's ethnographic research identified individual and practice-level barriers that slow the adoption of genomic testing. Some arise from the explosion of knowledge. Oncologists are hard-pressed to keep up with the exploding world of genome-related advances, and many oncologists outside academic settings say they treat the full spectrum of cancers.

"As a general oncologist, we have to know basically about 97 percent of all cancer treatments. Whereas a specialist at a university who only deals with one kind of cancer, they have to know 100 percent about one thing. I think it's much harder to know 97 percent about everything than 100 percent of one topic."
- Community oncologist, US

Because the field is still maturing, the tools that can help clinicians understand, address, and manage genomic-related data are generally immature or not widely available. Compounding the problem, genomic results are not typically integrated into electronic health records (EHRs) or clinical decision support systems (CDSS). This adds to the clinician's cognitive burden and slows productivity. Because relevant data is distributed across different systems, oncologists must take additional effort to integrate the genomic analysis results with imaging data, pathology diagnoses, molecular data, and other information needed for diagnosis and treatment planning.

"Sometimes, the results from different methods conflict with each other. We can hardly understand the reasons."
- Oncologist, PRC

Oncologists in both the PRC and the US rely heavily on reports from external labs and service providers to interpret genomic test results and identify recommended clinical actions *(Table 1)*.

Although single-marker and panel testing yield more specific results and clinical recommendations, NGS often provides additional information about molecular variants about which little or nothing is yet known. These "results of unknown significance" are perceived by oncologists as unhelpful clinically. In fact, many feel they make the oncologist's job more difficult, because they require more time to interpret and explain at a time when patients are already feeling overwhelmed. Oncologists must also determine how (or whether) to communicate genomic findings about these variants that may create stress for the patient but offer no new paths to treatment. So, while NGS may advance research and lead to new treatment options in the future, oncologists are reluctant to order the tests because their priority is to care for the patients in front of them today.

	ACADEMIC MEDICAL CENTER (N=12)	COMMUNITY PRACTICE (N=27)
Oncologist relies entirely on the report from an external lab	**42%**	**45%**
Oncologist consults with pathologist in practice or organization	**33%**	**33%**
Oncologist personally does additional research beyond the report	**25%**	**22%**

Table 1. Survey Results: Interpreting Genomic Results (US)

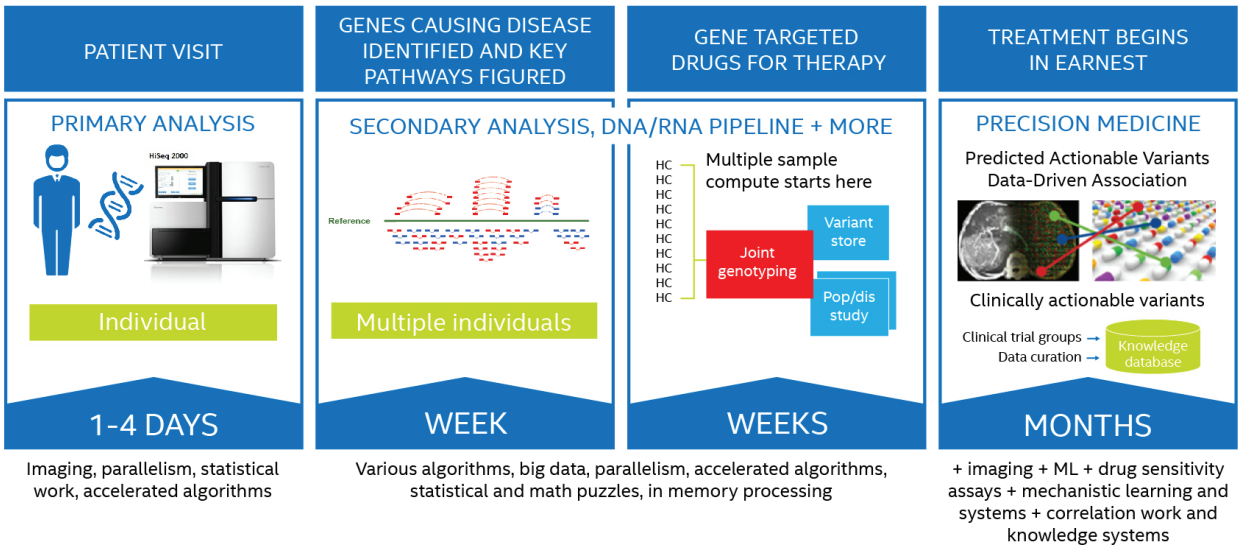

Figure 2. Today's Genome Analytics Pipeline: Waiting Weeks or Months for Treatment to Be Identified

Finally, the full process of genome sequencing and analysis can take weeks even with today's powerful technologies *(Figure 2)*. This is far too long, especially for patients with fast-growing cancers. It can force oncologists to begin treatment and then adjust if necessary once the NGS results are in hand.

Patients' Perspectives

Interviews with cancer survivors in the US and the PRC confirmed that most patients are unfamiliar with the possible benefits of genome sequencing and targeted therapy.

"Before going through all the processes, we know nothing about genetic data or target therapy. Now I know more from my friends and the oncologists. I think more education needs to be done here for patients and let more people know about them."
- Husband of a cancer survivor, PRC

They lack basic information such as the differences between genetic risk testing (which assesses a person's chance of inherited susceptibility to a given cancer) and genomic sequencing (which identifies the molecular nature of a cancerous tissue).

Because many cancers have no early screening tools, the diagnostic process isn't initiated until patients experience persistent symptoms. Once testing is initiated, factors such as scheduling delays, delays in evaluation of sequencing and other test results, and testing inaccuracies can prolong the diagnostic process. These delays, along with the lack of early screening tools, can contribute to a missed diagnosis or a later-phase diagnosis requiring more intense treatments. They also add stress for patients and loved ones.

Receiving a cancer diagnosis leaves patients and their loved ones feeling confused, overwhelmed, and anxious. They may have difficulty processing complex information relating to genome sequencing during this very stressful time. They need education to understand the genomic results and treatment options, but education takes time, and oncologists are perpetually time-constrained.

Most patients lack of familiarity with genome sequencing and its possible benefits, so are unlikely to advocate for its use. They are dependent on their provider for the information who, for the previously described reasons, may offer testing only in limited circumstances or only after traditional treatments fail. Although providers will answer questions when asked, many patients simply don't know what questions to ask.

"I think you would have to know the questions to ask. And at that point, you don't know enough about the disease."
- Cancer survivor, US

Removing Roadblocks

Identifying the issues suggests a variety of actions to address them. These actions must bring together patients, policymakers, life science and healthcare organizations, payers, and technology innovators to establish ethical, patient-centered policies and solutions.

Interrupting the Cycle of Inaction

Interrupting the cycle of inaction is essential to faster translation of next-generation genome sequencing from research to clinical environments. Policies that provide incentives for NGS and targeted therapies can help establish the evidence for early-stage, genomic analysis for cancer. As more sequencing is performed and outcomes tracked, the accumulation of evidence should aid in establishing NGS as standard care and encouraging payers to cover it.

In gathering and analyzing relevant data, governments, payers, and researchers will want to consider both business and clinical benefits of NGS. How are outcomes affected? What is the impact of getting patients and caregivers back on the job more quickly? How many duplicate or unnecessary diagnostic procedures can be eliminated? How many unnecessary treatments can be avoided? What is the impact of these changes? Analysts will need to examine difficult-to-quantify benefits such as reduced anxiety and suffering, as well as the economic benefits for patients, caregivers, healthcare systems, and societies.

The PRC's NHFPC is taking steps to address these issues and expand the successful use of NGS testing. In addition to approving the pilot hospitals for NGS application, the NHFPC is implementing or considering changes such as:

- Standardizing the pricing of NGS examinations.
- Establish cross-organizational quality guidelines for labs performing NGS.
- Nominating groups of leading oncologists or physicians to lead clinical practices of applying genomic data and data analysis on diagnosis and treatment of different diseases.
- Developing standard data formats for NGS reports, to encourage future data sharing.
- Exploring standards for clinical usage of NGS and defining workflows for using genetic sequencing and data analysis in cancer care.

Expanding Actionable Options

NGS grows in value as the number of targeted therapies expands—and while dozens of targeted therapies exist, many more are needed. Precision health analytics—which enable researchers to efficiently evaluate massive volumes of genomics and other data—can drive biomedical innovation that results in new compounds, determine what current treatments are most effective, and help identify additional uses for existing treatments.

Research organizations and funders should invest in increasing the number of actionable options from genomic sequencing. This can include basic research that leads to new understanding of cancer's biology, as well as work that builds on these findings to develop new medicines. Research can also identify genetic variations of different populations and subgroups that lead to precision medicine in the form of localization of treatments for specific regions or populations. For example, in China, more than 30 percent of lung cancer patients have the EGFR mutation, which occurs in only 20 percent of US patients with lung cancer. The high rate of EGFR mutations in the Chinese population makes this mutation an especially promising treatment target.

Patients can support this effort by advocating for research and development, and by participating in national efforts to sequence a larger portion of the population, since each person sequenced adds a new piece to the puzzle of cancer.

Collaboration is essential for clinical decision-making and for addressing the complex scientific and analytics challenges that lead to new therapies. Data sharing arrangements must support these collaborations while protecting patient privacy and safeguarding patient rights. In addition, using industry standards and open source technologies can help avoid the closed-system data silos that make collaboration and innovation more difficult.

Empowering Oncologists and Patients: Tools, Information, and Faster Results

Oncologists identified a number of changes that can address make it more practical to incorporate genomic analysis into their clinical workflows. Consultant labs can add significant value by offering more thorough interpretation of genomic results, including more information on clinical trials and other actionable information *(Table 2)*. High-quality patient education materials are sorely needed.

Faster genomic results are essential to speed treatment planning, reduce stress for patients and families, and reduce the need for start-and-stop treatments.

Integrating genomic analysis into EHRs, CDSS solutions, and other clinical applications can improve productivity and enable clinicians to base their care on a more comprehensive understanding of the patient's health. From a policy perspective, there is still discussion over whether genetic data is too sensitive to be integrated and stored with clinical data. However, US oncologists see clear value in this integration. Many are currently scanning genomic tests results into patients' records, and would welcome greater electronic integration.

"Testing is done in a variety of different ways across a variety of different platforms... and there's still not a single, easy way to categorize all that information...and keep it in a sortable, searchable form."
- Oncologist, US

DESIRED CAPABILITY	ACADEMIC MEDICAL CENTER (N=12)	COMMUNITY PRACTICE (N=27)
More information on clinical trials	75%	48%
Concise summary of actions to take	67%	63%
Greater detail about each variation or mutation	58%	63%
Embedded links to research reports	50%	37%
Integrate with EHR	50%	30%
Patient education materials	25%	33%

Table 2. Features to Improve Genomic Analysis Reports (US Oncologists)

Patient voices must inform every aspect of the unfolding genomics revolution. Patient advocacy groups have important roles to play in spreading awareness of the potential value of genomic testing, ensuring that patients benefit from their genetic data, and encouraging the development of patient-facing educational materials.

"Patients need guidance. They don't understand what you're talking about, and even for a lot of physicians that are not in our field, they don't understand. I think it just takes so much time in explaining this to them, and the more I say, the more they're confused. … How can we design a tool to help people understand better? Do we need some kind of picture, graph, or even a video or some animated something, a cartoon – that may be helpful." - Oncologist, US

As genomic analysis becomes more accepted as standard of care, advocacy groups may want to push for the development of tools to support self-advocacy. These might include easy-to-access information on relevant clinical trials, or interactive tools that compare treatment outcomes for people who most closely match the patient's genomic profile, environment, and more.

Intel's Role: Innovating and Collaborating for All in One Day

Computational technologies and tools are crucial to genome analytics. Intel® technologies run today's sophisticated genome sequencers, drive the analytics pipeline, and power research that leads to treatment breakthroughs. Advanced software—from deep learning analytics to 3D molecular dynamics simulations—uses each new generation of hardware to provide faster results, deliver more sophisticated insights, and create the next treatment breakthroughs. But as the amount of data skyrockets and the demand for genomics analysis grows, more powerful solutions are urgently needed.

Intel is actively working to meet these demands and deliver All in One Day precision medicine in 2020.[3] On the technology front, we've developed Intel® Scalable System Framework (Intel® SSF), a new architectural framework designed to deliver breakthrough performance for 3D biomedical models, life sciences simulations, and health analytics. We're introducing a wide range of innovative technologies that are built to handle rapidly growing volumes of data, answer increasingly sophisticated queries, and simulate more complex biomedical processes.

Beyond technology innovations, Intel is collaborating with health and technology leaders to develop and modernize important tools for life science research and clinical care. Intel and Oregon Health & Science University (OHSU) have established an open-source-based analytics platform for precision medicine, the Collaborative Cancer Cloud. The Cancer Cloud, which has since been joined by the Dana-Farber Cancer Institute and the Ontario Institute for Cancer Research, speeds genomic sequencing and enables medical institutions to securely share insights from their private patient genomic data for potentially lifesaving discoveries.

Intel is also continuing its ethnographic research to facilitate the design of user-centered solutions for All in One Day.

Scaling Genomics for Cancer Care and Beyond

Genome sequencing is an important step toward a precision medicine revolution that promises new approaches to diagnosing, treating, and preventing cancer and other diseases. Nations that take full advantage of precision medicine will be positioned to not only transform cancer care, but also build healthier, more productive societies. Healthcare organizations that put themselves on the forefront of precision medicine can deliver state-of-the-art care while enhancing patient satisfaction and advancing the science of medicine.

Healthcare leaders, patients, policymakers, governments, and innovators all have a stake in the success of these efforts, we all have important contributions to make. Policies and actions to interrupt the cycle of inaction—to gather data, build evidence, advance the computational infrastructure and make NGS the standard of care for cancer patients—move all of us closer to making All in One Day a reality, and ushering in transformative era of precision health and wellness. Please join us.

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Learn more about All in One Day and Intel technologies. Talk to your Intel representative, or visit us on the web:

- www.intel.com/content/www/us/en/healthcare-it/life-sciences.html

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