REVIEW ARTICLE

FRONTIERS IN MEDICINE

Genome Sequencing during a Patient's Journey through Cancer

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A CANCER DERIVES FROM A CLONE OF SOMATIC CELLS THAT HAS ESCAPED from the built-in constraints governing healthy cellular function, leading to uncontrolled proliferation, tissue invasion, immune evasion, and the reshaping of the local tissue microenvironment.[1] Many of these cellular properties arise from somatic mutations that accumulated in the cancer clone throughout life. Modern DNA sequencing methods have enabled complete genomic characterization of cancers on an unprecedented scale, leading initially to an improved understanding of cancer biology and, more recently, to clinical applications. These include improvements in cancer diagnosis and prognosis, identification of new therapeutic targets, decision support for therapeutic choices, and applications in disease monitoring. In this review, we explore what we have learned from systematic sequencing of cancer genomes. We discuss the current and potential future clinical applications of genome sequencing and reflect on both the promise and challenges around large-scale integration of genome sequencing into precision cancer medicine (see video).

Massively parallel DNA sequencing methods, also called "next-generation sequencing," enable the simultaneous analysis of millions of fragments of DNA. A sample from a patient's tumor can be sequenced alongside a sample of normal tissue, usually blood, from the same patient, allowing genetic variants to be identified and classified as either somatic mutations, found only in the tumor sample, or inherited (germline) polymorphisms, also present in the normal sample. Proof-of-principle studies showed the feasibility of identifying all somatic mutations acquired by the cancer clone.[2-4] These studies have now been followed by analyses of data from tens of thousands of patients,[5] generating wide-ranging insights into cancer biology (Fig. 1).

Initial clinical implementation of massively parallel sequencing has typically involved so-called targeted sequencing, selecting either for the approximately 300 to 600 genes known to cause cancer or for all protein-coding genes, which account for approximately 1% of the genome. The main advantages of targeted sequencing are lower costs and deeper analysis of specific regions of the genome known to be most important for cancer biology. However, as costs of sequencing further decrease, sequencing of the entire 3 billion base pairs of the genome will probably emerge as the standard, since this would make it possible to identify all types of mutation in all regions of the genome.[6]

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A video overview of genome sequencing in cancer and an illustrated glossary are available at NEJM.org

BIOLOGIC AND CLINICAL INSIGHTS FROM CANCER GENOMES

SOMATIC MUTATIONS THAT DRIVE CANCER

Among the thousands of somatic mutations acquired by a cancer cell, growing evidence suggests that only a handful actually instruct the cell to function as an autonomous clone — these we call driver mutations. The remaining mutations are termed

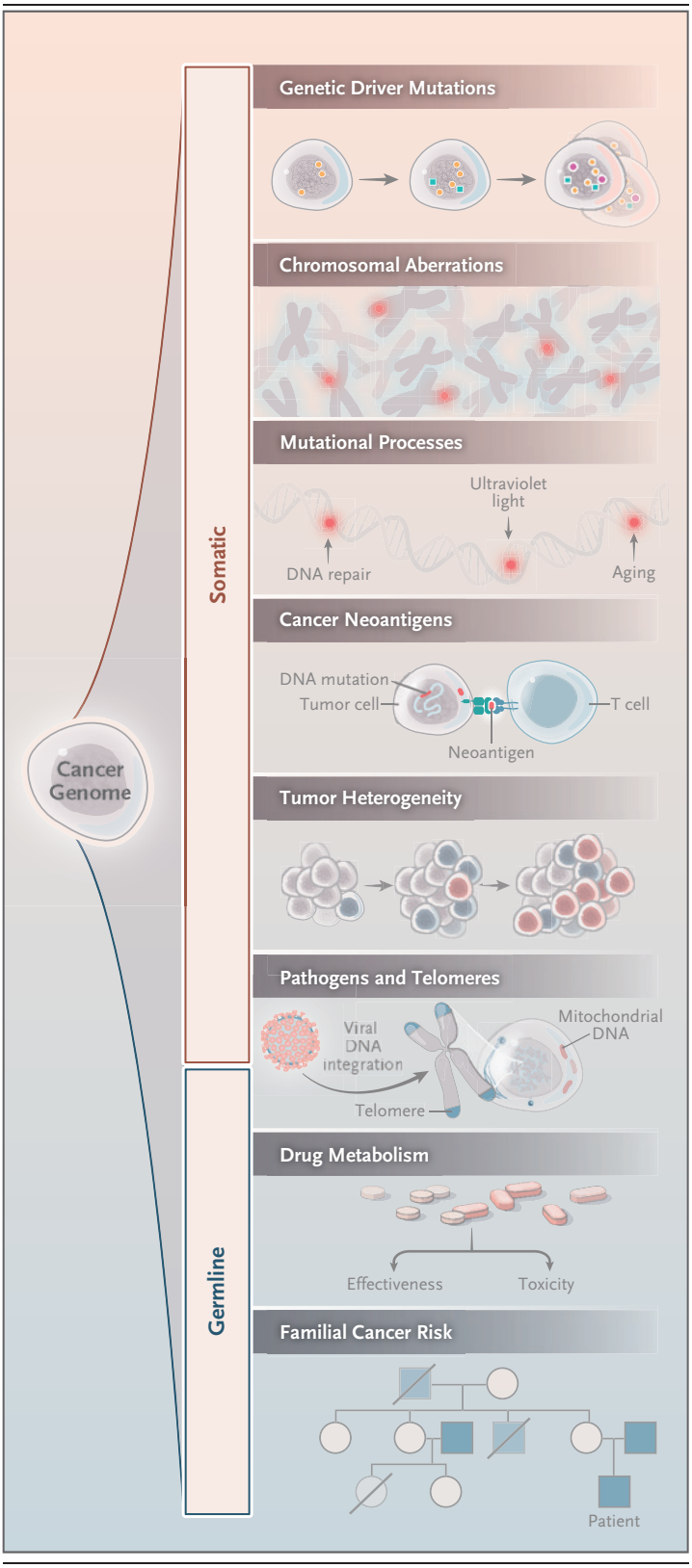


Figure 1. Insights from Studying the Cancer Genome.
Sequencing a patient's cancer provides insights into many facets of tumor biology. These include features acquired as somatic alterations by the cancer clone, such as driver mutations, large-scale chromosomal abnormalities, and mutations recognized by the immune system (neoantigens). In addition, inherited factors can also be assessed, such as familial cancer risk and variants affecting the metabolism of therapeutic agents used to treat cancers.

"passenger" mutations, acquired by the clone before the first driver mutations arose or during or after its subsequent transformation. Driver mutations can take many forms, including substitutions of one base of DNA for another, insertions or deletions of small numbers of DNA bases, gains or losses of large chromosomal regions or even whole chromosomes, and rearrangements that fuse one gene to another or juxtapose one gene with the regulatory apparatus of another. Even though the protein-coding content of the human genome is only 1%, the vast majority of driver mutations fall within this portion, with approximately 300 to 600 of the more than 20,000 protein-coding genes being targets for driver mutations.[7-11] A few driver point mutations in non–protein-coding regions of the genome have been identified,[12-16] but with less frequency than protein-coding drivers.[17,18]

Although we have an increasingly complete catalogue of cancer genes affected by driver point mutations, gene fusions, and simple chromosomal rearrangements, understanding how to interpret large-scale complex chromosome rearrangements is more difficult. Such changes can affect multiple genes simultaneously, and it is likely that their oncogenicity arises from an aggregate excess of cancer-promoting over cancer-suppressing alterations.[11,19] Driver mutations tend to accumulate gradually over time, with a cancer often requiring decades to acquire the full complement of cooperating events.

Because driver mutations are causative, drugs that target the function of resulting proteins can be therapeutic. For example, imatinib targets the BCR–ABL fusion protein in chronic myeloid leukemias.[20] The development of imatinib was followed by the development of BRAF inhibitors for *BRAF*-mutant melanoma,[21] EGFR inhibitors for non–small-cell lung cancers,[22,23] anaplastic lym-

phoma kinase (ALK) inhibitors for lung cancers with *ALK* fusions,[24] and anti–human epidermal growth factor receptor 2 (HER2) antibodies for HER2-amplified breast cancers.[25] All these therapies can block the impetus of a cancer at its source.

MUTATIONAL PROCESSES IN CANCER

Somatic mutation can arise from both endogenous and exogenous mutational processes. Exogenous mutagens include chemicals (e.g., tobacco, aflatoxin B_1, and chemotherapeutic agents), ionizing radiation, and ultraviolet light, all of which damage DNA, generating mutations when damaged bases are incorrectly repaired or copied. Mutations can also arise from cell-intrinsic processes, such as errors that occur during DNA replication, reactive oxygen species, impaired DNA repair, and the activity of viruses. Many of these cell-intrinsic processes occur at a constant rate throughout life, leading to linear accumulation of mutations with increasing age.[26,27]

DNA damage arising from mutational processes often enriches in particular DNA sequences, creating distinctive signatures in the cancer genome.[28,29] More than 30 such signatures have been identified — some understood, some mysterious.[29] These mutational signatures can specify whether a lung cancer came from a tobacco smoker or nonsmoker,[30] whether a hepatocellular carcinoma arose through exposure to the carcinogen aflatoxin B_1,[31] how ultraviolet light has shaped a melanoma,[32] and whether mutations in *BRCA1* or *BRCA2* caused an ovarian cancer.[33,34] Beyond point mutations, there are also many signatures of large-scale chromosomal abnormalities, again arising from a mix of external and endogenous processes.[35-40]

Clinically, mutational signatures can aid therapeutic decision making. A deficiency in mismatch repair massively increases mutation rates, generating variants recognized by the immune system. As a result, these tumors, which have characteristic mutational signatures,[29] can have impressive responses to immunotherapy.[41] A deficiency in homologous recombination through loss of BRCA1 or BRCA2 causes cancer cells to become dependent on other DNA repair pathways, leading to distinctive mutational signatures[33,34] and vulnerability to inhibition of those other repair pathways.[42] Poly(adenosine diphosphate–ribose) polymerase (PARP) inhibitors, which kill cells with DNA breaks, have activity in breast, ovarian, and pancreatic cancers among carriers of *BRCA1* or *BRCA2* mutations.[43-45] Mutational signatures of homologous recombination deficiency are seen in these tumor types beyond those with loss of *BRCA1* or *BRCA2*,[33,34,46] which suggests that other patients may also benefit from such therapy.

TUMOR HISTORY AND INTRATUMOR HETEROGENEITY

Within individual tumors, substantial genomic diversity exists among the cells, resulting from ongoing mutational processes and Darwinian selection for fitter subclones of tumor cells. Clonal structures of tumors can be reconstructed with the use of genome sequencing.[47-51] Some tumor types, such as clear-cell renal cancer[48,52-54] and colorectal cancer,[55,56] acquire driver mutations in a particular order, whereas others, such as breast[57,58] and lung[59,60] cancers, show multiple routes of evolution. Metastasis, when it occurs, typically arises through dissemination late in the evolution of the primary tumor.[49,53,61-63]

How to use information about the clonal diversity of a cancer in clinical practice remains uncertain. Different regions of a primary tumor — or, indeed, metastatic deposits — may harbor different driver mutations, which complicates therapeutic decision making.[48,61] Proof-of-principle studies have shown that tumors with higher subclonal diversity are associated with a worse prognosis,[54,59,64] and driver mutations can change the prognosis even when they represent a small proportion of tumor cells.[65] An important application will be the prediction of the likelihood that a cancer harbors a drug-resistant subclone; such predictions would be facilitated by serial monitoring of tumors. Mutations conferring drug resistance often predate targeted therapy.[66-68] For example, minor clones in blood with *TP53* driver mutations can expand after chemotherapy to seed therapy-related leukemia.[68]

NEOANTIGENS IN CANCER

Our immune system is actively engaged in surveillance to protect against tumor development. Somatic mutations within a cancer result in the generation of new peptides, termed neoantigens, that can be recognized as "nonself" by the immune system. As might be expected, the neoantigen load is higher in tumors with a higher mu-

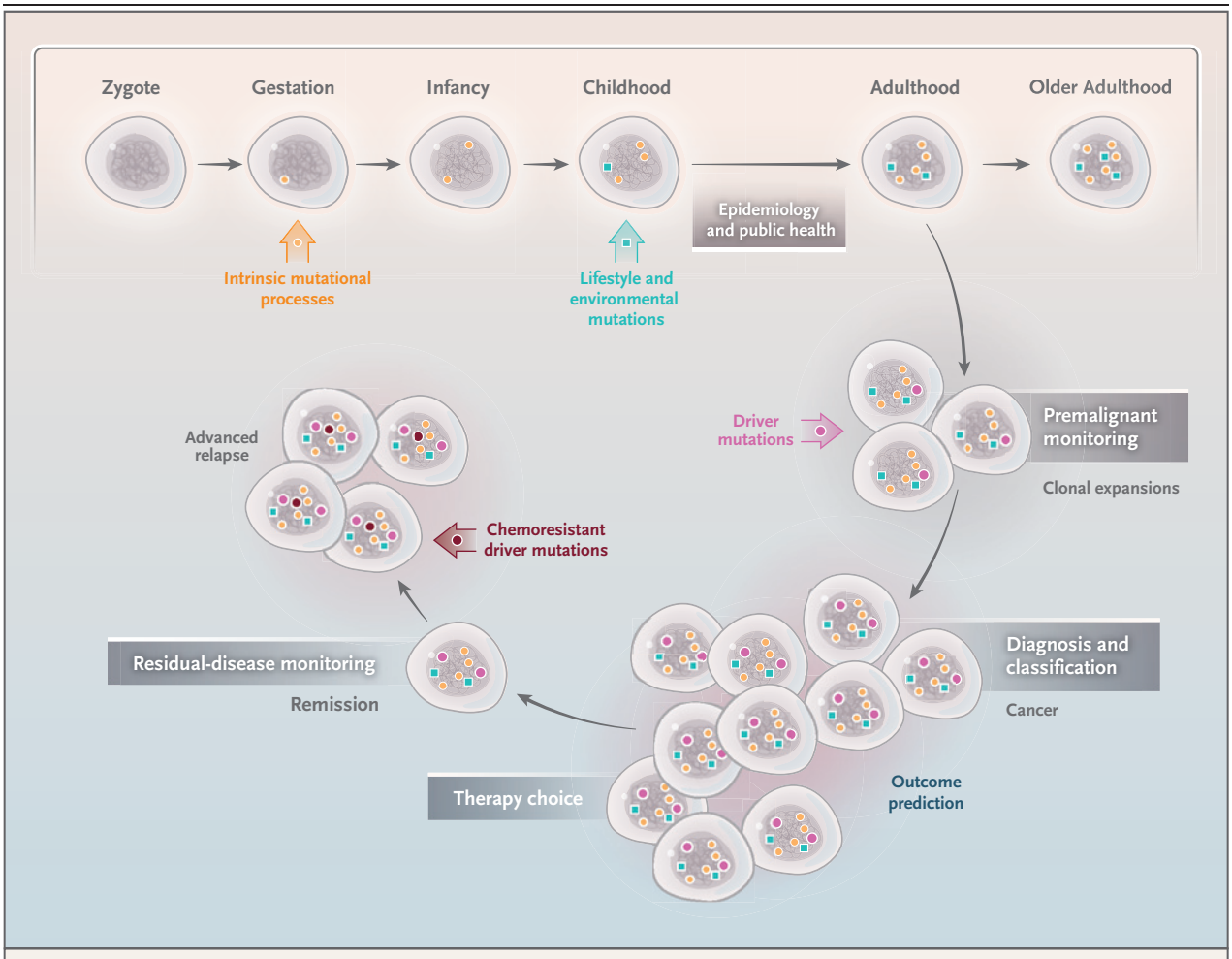


Figure 2. Genome Sequencing Opportunities for Cancer Management.

A cancer can trace its lineage back through a series of cell divisions to the fertilized egg. Genome sequencing has the potential to influence cancer-management strategies at many stages of this gradual process of transformation to cancer. These include public health initiatives to prevent cancer, early intervention before a cancer becomes invasive, and strategies for the diagnosis, classification, treatment decision support, and monitoring of established cancers.

tational burden,[69,70] and evidence is increasing that tumors with an elevated neoantigen load respond better to immunotherapy.[41,69,71] Improved characterization of neoantigens in cancer is shaping how we use immune-checkpoint inhibitors and is refining other forms of immunotherapy, such as chimeric antigen receptor T cells[72] and cancer vaccines that explicitly target neoantigens.[73]

OPPORTUNITIES FOR GENOME SEQUENCING OVER A PATIENT'S LIFETIME

The causal role that mutation plays in cancer biology means that sequencing the genome offers opportunities to shape cancer therapy at multiple time points during a patient's care pathway (Fig. 2).

PREDICTING FUTURE RISK OF CANCER FROM THE GERMLINE GENOME

The inherited (germline) genome can be interrogated at any stage of life, enabling prediction of a person's risk of having a cancer in the future. Currently, screening for high-penetrance inherited variants is undertaken in families with clusters of particular tumor types, with more than 100 high-penetrance cancer-predisposition genes known.[74] Many cause specific tumor syndromes, such as *VHL* mutations driving hemangioblastomas and renal cancers,[75] but many high-penetrance

germline variants increase the risk of a broader range of cancers than classically described.[76]

High-penetrance pathogenic variants are found in 5 to 10% of unselected patients with cancer,[76] but most inherited predisposition can be attributed to thousands of alleles commonly present within the population that individually provide only a slightly increased risk of cancer. The best-characterized cancers now have more than 100 genomic regions associated with risk, accounting for more than 15 to 20% of familial relative risk.[77,78] Polygenic risk scores for a given cancer can be calculated by aggregating these many low-penetrance variants, with persons in the top percentiles of risk nearing the relative risks associated with single high-penetrance genes.[78] The germline genome can also be used to identify patients at risk for toxic effects from chemotherapy because of variation in drug-metabolizing enzymes.[79]

Knowing that a patient has a high-penetrance variant will typically trigger intensive screening programs, prophylactic surgery, or both — such strategies have improved outcomes in patients with Li–Fraumeni syndrome or inherited *BRCA1* or *BRCA2*, for example.[80,81] The way in which polygenic risk scores should be incorporated into individualized cancer screening programs is less clear but will become increasingly important to determine as direct-to-consumer germline testing becomes widespread.

EPIDEMIOLOGY AND PUBLIC HEALTH

That mutational signatures can act as a fingerprint for exogenous carcinogens[82] heralds a new wave of "molecular epidemiology." Incidence rates for many cancer types vary globally by orders of magnitude, although the cause of this variability is unclear. Genomes of tumors from high-incidence and low-incidence regions may reveal occupational or lifestyle exposures responsible for this variation. This potential is exemplified by emerging data showing the effect of the mutagen aristolochic acid in regions with high incidences of renal tract and hepatic cancers. The aristolochia plant, from which aristolochic acid derives, is used as an herbal medicine, especially in East Asia, and grows wild along the Danube basin, where it contaminates wheat harvests.[83] Most renal tumors in Romania[84] and a large minority of liver and urinary tract cancers in East Asia[85-87] have thousands of mutations with a mutational signature exactly replicated by exposing cells to aristolochic acid in vitro.[82] Coupled with epidemiologic data, the case for aristolochic acid being a major causal agent of cancers in these regions is spurring public health initiatives to reduce exposure.

STRATIFICATION FOR INTERVENTION AT PREMALIGNANT STAGES

Many cancers pass through recognizable early stages of disease — the aim of screening programs is to identify and treat such cancers before they become incurable. However, not all early-stage lesions will shorten a patient's life, so there is a risk of overtreatment. Genome sequencing of early cancer lesions may help stratify which lesions are likely to progress and which could be safely monitored without initial intervention. For example, approximately half of high-grade squamous dysplasias and carcinomas in situ of the bronchus progress to invasive carcinoma, but a third spontaneously regress. Those that progress carry a higher mutation burden, more copy-number changes, and more driver mutations than those that regress,[88] which suggests that it may be possible to identify which lesions need early intervention. Similarly, approximately 10 to 20% of healthy persons older than 70 years of age have clones in their blood that have the first driver mutations of a myeloid cancer[89-92] — integration of clinical, laboratory, and genomic features can suggest which of these patients are most likely to have progression to acute myeloid leukemia.[93] Large-scale studies are under way to assess the predictive value of the genomic changes seen in other early neoplasms, such as Barrett's esophagus,[94] intermediate-risk prostate cancer,[95] and breast ductal carcinoma in situ.[57] These proof-of-principle studies, although not yet ready for clinical implementation, presage an era of more personalized early intervention for cancer.

CANCER DIAGNOSIS

Certain somatic mutations are pathognomonic for specific cancers, which suggests that they can be used for diagnostic purposes. Clinical testing for such mutations is best exemplified in hematooncology, in which identification of mutations such as the *JAK2* V617F mutation or a *BCR–ABL* translocation in blood tests confirms an underlying myeloid neoplasm,[96] thus simplifying diag-

nostic pathways and often avoiding invasive biopsy. For solid tumors, genome sequencing may facilitate interpretation of small presurgical biopsies, especially fine-needle aspirations in which histologic analysis may be inconclusive. For example, gene sequencing of thyroid nodule specimens obtained by fine-needle aspiration can distinguish benign from malignant nodules.[97] Genome sequencing may also identify the tissue of origin and potential therapeutic targets in carcinomas of unknown primary site,[98] and algorithms that incorporate patterns of driver mutations and mutational signatures are increasingly accurate for this application.[99]

TUMOR CLASSIFICATION

Classification systems strive to group cancers into categories, such that clear distinctions are defined between, and similarities are defined within, individual subgroups. In current clinical practice, tumors are classified according to tissue of origin, histologic category, and stage — these classifications provide a universal language for describing both an individual patient's cancer and cohorts in clinical trials. As the catalogue of mutations driving common cancers reaches completion,[5] we anticipate that cancers will receive a categorization according to their genomic features, alongside their histologic type and tumor–node–metastasis stage.

Driver mutations do not assort randomly among patients with a particular tumor type, with some pairs of cancer genes tending to be comutated in the same samples and others almost never mutated together in the same patient.[100] As a result, a tumor type can be compartmentalized such that driver mutations are most concordant among patients within each subgroup and different among subgroups. Such schemes are well advanced in blood cancers, such as acute myeloid leukemia[65] and myeloproliferative neoplasms,[101] but are also emerging in solid tumors, such as breast cancer,[102,103] medulloblastoma,[104] and pancreatic cancer.[46]

A genomic classification has the advantage that it groups tumors on the basis of disease-causing driver mutations and is thus inherently linked to disease biology, ensuring long-term stability and reproducibility of the classification. Patients with similar genomic features tend to have similar clinical features and therapeutic responses, evidenced by improved outcomes for *PML–RARA*–positive acute myeloid leukemia and *HER2*-positive breast cancer with therapies targeting their defining driver mutations.[105,106]

PREDICTING PATIENT OUTCOME

Given their causative role in disease biology and the considerable variability in distribution among patients, driver mutations contain much information about the future clinical course of a cancer. Much of this information is orthogonal to clinical variables,[65,101,103,107] and prognostic accuracy is therefore increased by combining clinical and genomic data. The prognostic associations of individual genes tend to be specific to particular tumor types, such as *SF3B1* mutations conferring a good prognosis in myelodysplasia[108] but a poor prognosis in chronic lymphocytic leukemia.[14] However, some general principles do emerge — for example, *TP53* mutations typically worsen prognosis, genomic instability and extensive copy-number variation are usually associated with more aggressive or treatment-resistant tumors, and survival generally deteriorates with increasing numbers of driver mutations.[14,64,65,101,102,109-112]

In current clinical practice, many treatment decisions are based on patients' predicted outcomes, whether that is judged according to stage, grade, or genetics: for example, decisions about whether to use adjuvant chemotherapy for colorectal cancer depending on stage, active surveillance or surgery for localized prostate cancer depending on Gleason score, and stem-cell transplantation or intensive chemotherapy for acute myeloid leukemia depending on whether high-risk driver mutations are present. Estimating prognosis underpins these therapeutic choices because of the implicit calculation about whether the improvement in prognosis justifies the increased risks of toxic effects from more intensive treatment.

Genome sequencing facilitates prognostic estimates that are personally tailored to the individual patient. Such estimates will depend on building "knowledge banks" comprising individual patient data from large cohorts and encompassing molecular profiling, clinical variables, histologic analysis, and staging, coupled with treatment and outcome data.[65,93,101,103,107] Beyond a one-dimensional prediction of survival probability, such personally tailored predictions can assign probabilities to different clinical journeys, such as distant relapse, locoregional relapse, or disease-free survival in patients with

breast cancer[103] and leukemic transformation or long-term survival in patients with myeloproliferative neoplasms.[101] Such information is particularly useful in decisions about treatment intensity — allogeneic stem-cell transplantation in acute myeloid leukemia, for example, can be offered more cost-efficiently to those most likely to benefit if genomics-based precision prognoses are used.[107]

PRECISION CANCER TREATMENT

The identification of specific genetic alterations in tumors has helped develop and guide therapy. Tyrosine kinase inhibitors targeting the BCR–ABL1 fusion protein dramatically improve survival in patients with chronic myeloid leukemia.[20] Vemurafenib, an inhibitor of BRAF, frequently mutated in melanoma, has shown impressive responses in patients with metastatic melanoma,[21] although the responses are often transient owing to the emergence of resistant subclones. Resistance is a theme that emerges repeatedly in the field of targeted therapeutics and is mediated by a range of mechanisms, including mutations that abrogate binding of the small-molecule inhibitor,[113] acquired mutations in the same signaling pathway that bypass the drugged protein,[114,115] mutations that activate alternative proliferative signaling pathways,[116] and maintenance of a population of quiescent cells with epigenetically determined drug tolerance.[117] Knowing the likely mechanisms of resistance can enable preemptive therapy, evidenced by more durable responses of metastatic melanoma to combination therapy with BRAF inhibitors and inhibitors of MEK1 and MEK2.[118]

Despite the promise of targeted therapies, most cancer genomes do not have driver mutations for which a molecularly targeted agent is licensed.[10] Some tumor types, such as mesothelioma[119] and clear-cell renal carcinoma,[120] are dominated by driver mutations that inactivate genes, a notoriously difficult scenario for developing targeted therapeutics. Attacking such tumors relies on finding their specific vulnerabilities: high-throughput in vitro screens of drug libraries and genome editing are revealing unsuspected dependencies of cancers on particular genes that could be exploited therapeutically.[121-123]

New approaches in clinical-trial design — such as basket and umbrella studies, in which patients are directed to different therapies by virtue of the driver mutations of their cancers — have shown some occasional successes but overall have been disappointing.[124] However, thus far, such studies have involved relatively small cohorts,[125-128] and the clinical usefulness of genome-guided therapeutic choices remains unproven beyond specific indications such as those described above.

CANCER MONITORING

Of course, hematopoietic tumors can be detected directly in blood. In addition, many solid tumors shed fragments of their genome into the bloodstream,[129,130] as so-called circulating tumor DNA. This shedding is roughly proportional to tumor bulk, allowing both detection and quantification of tumor-specific mutations in plasma samples. Methods for quantifying known point mutations[131-133] and genomic rearrangements[134,135] present in the cancer enable early detection of relapsing clones, often months before clinical detection. Direct sequencing of plasma DNA may also identify clonal evolution and the emergence of resistance mutations while tumors are still in a state of minimal residual disease.[66,67]

Monitoring of tumor-specific genomic rearrangements is a cornerstone of precision therapy for hematologic cancers, enabling early intensification of therapy in patients with acute lymphoblastic leukemia that responds poorly to treatment[136] or the switching of therapy for rising *BCR–ABL* levels in patients with chronic myeloid leukemia.[137] Clinical trials have established the appropriate treatment paradigms with this molecular monitoring, and analogous trials will clarify the role of plasma DNA monitoring in the care of patients with solid tumors.

PERSONALIZATION OF CANCER CARE PATHWAYS

Currently, patient access to modern genomics is patchy across regions and countries, but as protocols for sample processing and data analysis become established, access will broaden. The debate about testing of gene panels as compared with whole-genome sequencing is transient and distracting — ultimately, there is little doubt that we will be sequencing whole genomes, and we should be building the logistic infrastructure to handle this in our health systems. This would have the added benefit of replacing many standalone tests used across cancer diagnostics that

Personal Details

Name	Test Patient
Date of birth	June 4, 1966
Sex	Female
Family history	None
Additional details	Thrombocytosis with anemia Splenomegaly, angina
Histology	Myelofibrosis
Therapy	None at present

Test Details

Sequencing	Whole genome
Platform	NovaSeq
Depth	50x

Sample Details

Accession No.	AC998203.47
Specimen type	Whole blood
Collection date	July 22, 2019
Receipt date	July 24, 2019
Processing date	July 27, 2019

Care Team

Scientist	Dr. Name and Date

Driver Mutations

Finding	*CALR* L367fs*46; *PPM1D* p.L450*; *TP53* pL194R; *GNAS* p.R201H; *TET2* p.?

Chromosomal Aberrations

Finding	No chromosomal abnormalities identified
Interpretation	Low-risk karyotype

Mutational Processes

Finding	Predominantly signature 1
Identification	Age-related mutational process No recognized external carcinogen effects No recognized abnormal DNA repair effects

Tumor Heterogeneity

Finding	Dominant *CALR*-mutated clone
Interpretation	Additional mutations appear to be subclonal

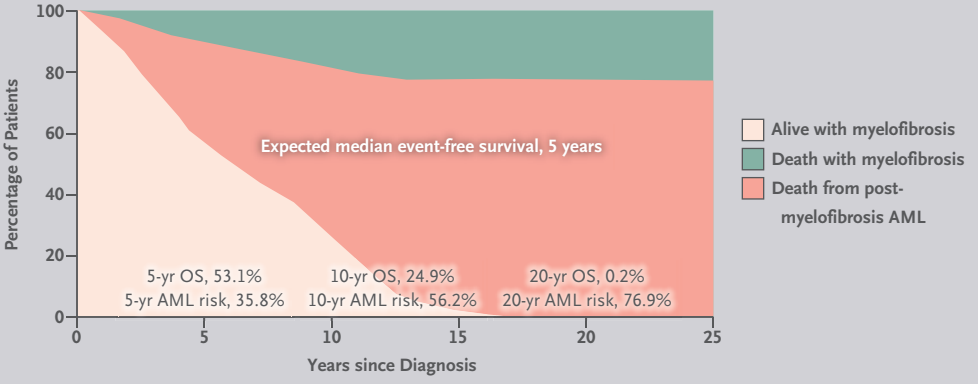
Familial Cancer Risk

Finding	No high-penetrance variants identified
Interpretation	No further familial screening required

Pharmacogenomics

Finding	Not requested
Interpretation	Not applicable

Knowledge Bank Prediction (MPN multistate, version 1.0)



Conclusions

The presence of a +1-bp frameshift mutation in *CALR* is pathognomonic for a myeloproliferative neoplasm (MPN). *CALR* mutations are found in traditionally defined essential thrombocythemia and myelofibrosis. Mutations in *PPM1D* and *TET2* can be found within the MPN clone as well as in age-related clonal hematopoiesis, and *PPM1D* mutations can be associated with previous exposure to chemotherapy. Mutations in *GNAS* are associated with a higher risk of disease transformation. The knowledge bank prediction takes into account patient age, clinical characteristics at presentation, and the somatic mutations present in the sample to make predictions of future patient survival and disease transformation. In this patient, this approach estimates a 53% chance of overall survival (OS) at 5 years and a 56% risk of transformation to acute myeloid leukemia (AML) at 10 years.

Figure 3. Future Cancer Genomics Report.

are separately developed, maintained, and standardized.

Imagining this empyrean of genomics in clinical oncology, we have mocked up a future diagnostic report of the genome from one of our patients with a myeloproliferative neoplasm (Fig. 3). Such reports will probably have an overall summary page with high-level interpretative content, linking out to supporting data and evidence. Maximizing the usefulness of these reports will require much supporting infrastructure, including the following:

A new generation of genomics scientists. These diagnostic laboratory scientists will understand technical aspects of genome sequencing and have fingertip access to databases containing genomic information.

Comprehensive quality-assurance and quality-improvement programs. Sequencing, analyzing, and interpreting cancer genomes is hard, and there is considerable variability in outputs among current providers — variability that can be ameliorated with national quality-assessment programs.[138]

Phase 4 clinical trials. Pivotal, phase 3 randomized trials are not powered to detect gene-specific benefits of experimental therapeutics, and we should develop systems for collecting detailed genomic and clinical-outcome data from patients receiving drugs after licensing.

Frameworks for building and maintaining knowledge banks. The collection, aggregation, and sharing of data will require national or international initiatives to amass patient data from clinical care and innovation in data storage and access.

Development, testing, and continuous improvement of decision-support algorithms. Physicians intuitively integrate performance status, prognosis, and therapeutic options for a given patient, a process that could be supported by accurate, up-to-date predictions from knowledge banks containing data from similar patients.

An ethical framework for the sharing and protection of genomic data. Engagement with the public and patients will be required to ensure that data management occurs in a transparent and responsible manner that protects patients' identity and respects individual wishes for privacy.

Nothing on this wish list is unachievable; indeed, state-of-the-art prototype programs are already operating on a regional or national scale and putting these building blocks in place. These programs have begun the process of transitioning cancer genomics from academia to a sustainable, routine, and, with time, universally accessible diagnostic test underpinning cancer care.

An audio interview with Dr. Campbell is available at NEJM.org

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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