



CORAL HEALTH

The Blockchain for Personalized Medicine

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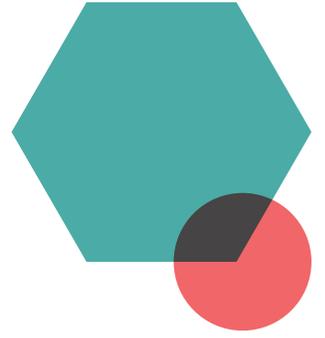
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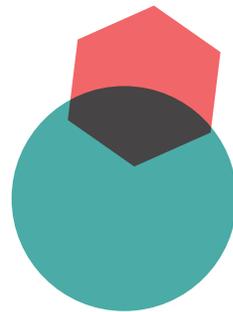
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1. INTRODUCTION



1.0 Introduction

Coral Health has recognized a significant disruption opportunity in global healthcare systems. Its vision will create efficiency gains in interactions between key actors in the healthcare domain, driving productive data sharing, greater profitability, and improved public health outcomes.

It is well known that in traditional healthcare delivery models, providers, laboratories, payers (i.e. insurance companies) and drug companies all store patient data in disparate formats and there is no standardization of record keeping. This has led to data breaches and the disarray we see today in health records exchange. Poor data sharing infrastructure has also been impeding the progress of drug discovery and public health research. Efforts to address this problem have largely focused on forcing the entire ecosystem to adopt a new, shared standard. These attempts have been unsuccessful because they've been quickly rebuffed by regulation, lobbying and patient apathy.

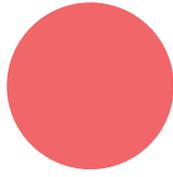
Coral Health's key differentiator in its expansion plan is that it targets small and readily addressable components of the health data domain, rather than attempting to create an immediate panacea. For example, it will cater to payers' incentives for quicker claims processing by allowing them to use smart contracts to automatically make prior authorization decisions. In this incremental fashion, Coral Health will create efficiencies in small but multiple parts of the current health data landscape, steadily moving towards its broader objective.

Coral Health uses blockchain technology to create an iterative, interoperable, accessible, secure, and scalable healthcare ecosystem. This new platform will permit patients to easily and securely share their medical records with providers, labs, payers, and other stakeholders – all while maintaining complete control over the privacy of their medical information. Coral Health will alleviate many of the problems faced by the current healthcare system, including the siloing of data, the incongruity of legacy databases, the challenges of analyzing unstructured data, prohibitively high administrative costs, the lack of data security, and unaddressed privacy concerns.

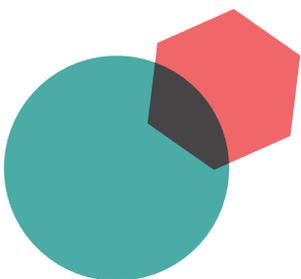
The current lack of efficient health data storage and sharing has prevented the widespread adoption of “personalized medicine,” the practice of customizing medical treatment to an individual's characteristics, needs, and preferences. Personalized – or precision – medicine has long been recognized as the future of health care, and industry operators have devoted significant resources to the development of personalized healthcare options, only to be stymied by the current system. The Coral Health ecosystem integrates the tools necessary to finally empower the widespread adoption of personalized medicine. These tools include an encrypted and distributed storage system that allows real-time access to medical data, built-in incentives that encourage data sharing, automation tools that will drastically reduce administrative costs, and precise permissions controls that ensure patients' privacy. Patients and other stakeholders will interact with the Coral Health ecosystem using tokenized, customizable applications initially published by Coral Health, and further built out by other developers on the platform. Stakeholders will be able to easily build powerful, flexible methods to process and digest their data, thereby simplifying operations, reducing administrative work, and improving care.

In the following paper, we will outline the current needs of the healthcare industry, the failings of the present system, and the solutions that Coral Health will provide by:

- Giving an overview of the state of personalized medicine
- Detailing the issues with the current healthcare system that prevent the adoption of personalized medicine
- Demonstrating how Coral Health offers solutions to these problems, and empowers the development of personalized medicine
- Outlining key use cases for the Coral Health system
- Overview of token economics and usage
- Giving a technical description of the blockchain technology that underpins the Coral Health ecosystem
- Detailing initial strategies to onboard patients, providers, labs, payers, pharmaceutical companies, and public health institutions, and
- Discussing Coral Health's roadmap and long-term vision.



2. CURRENT STATE OF PERSONALIZED MEDICINE



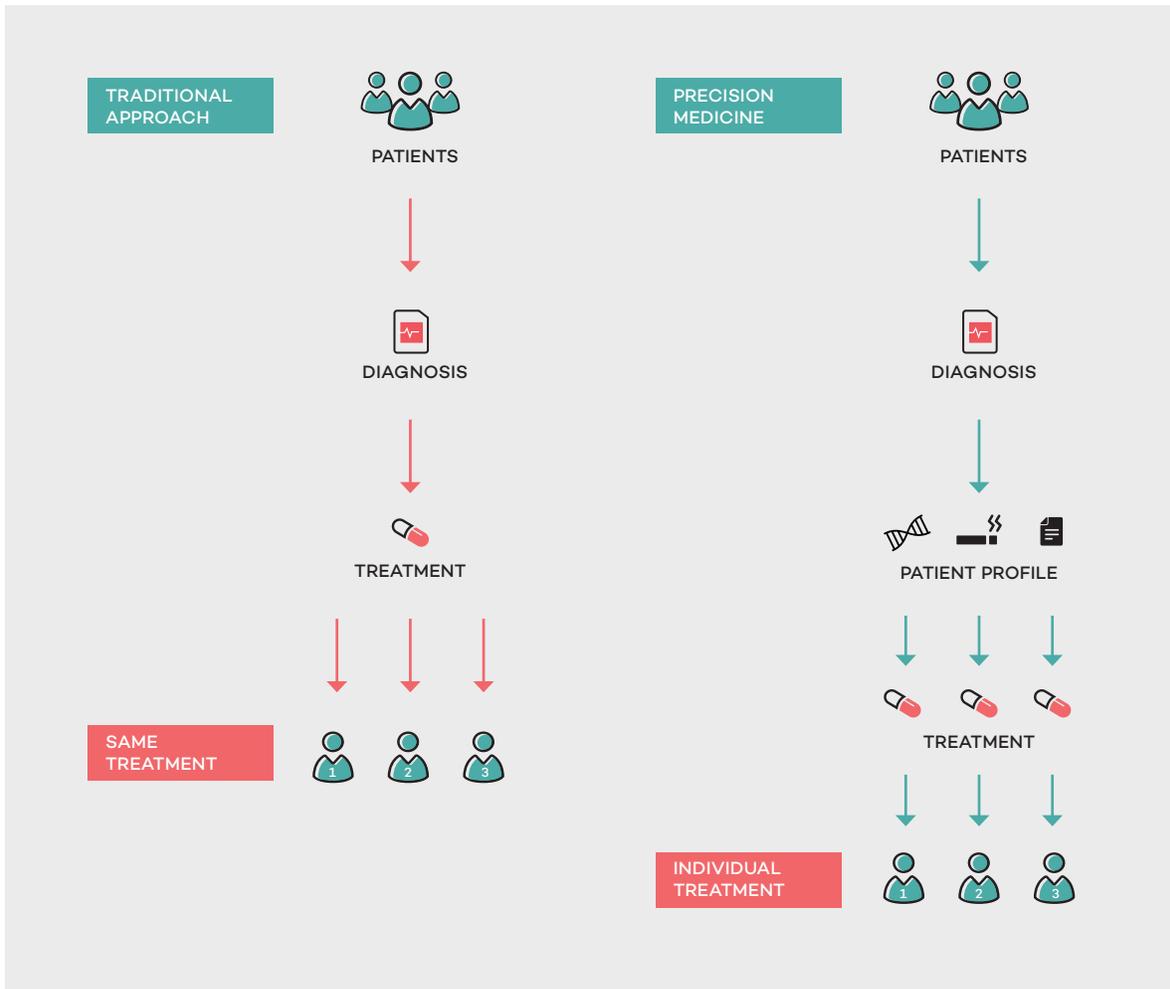
2.0 Current State of Personalized Medicine

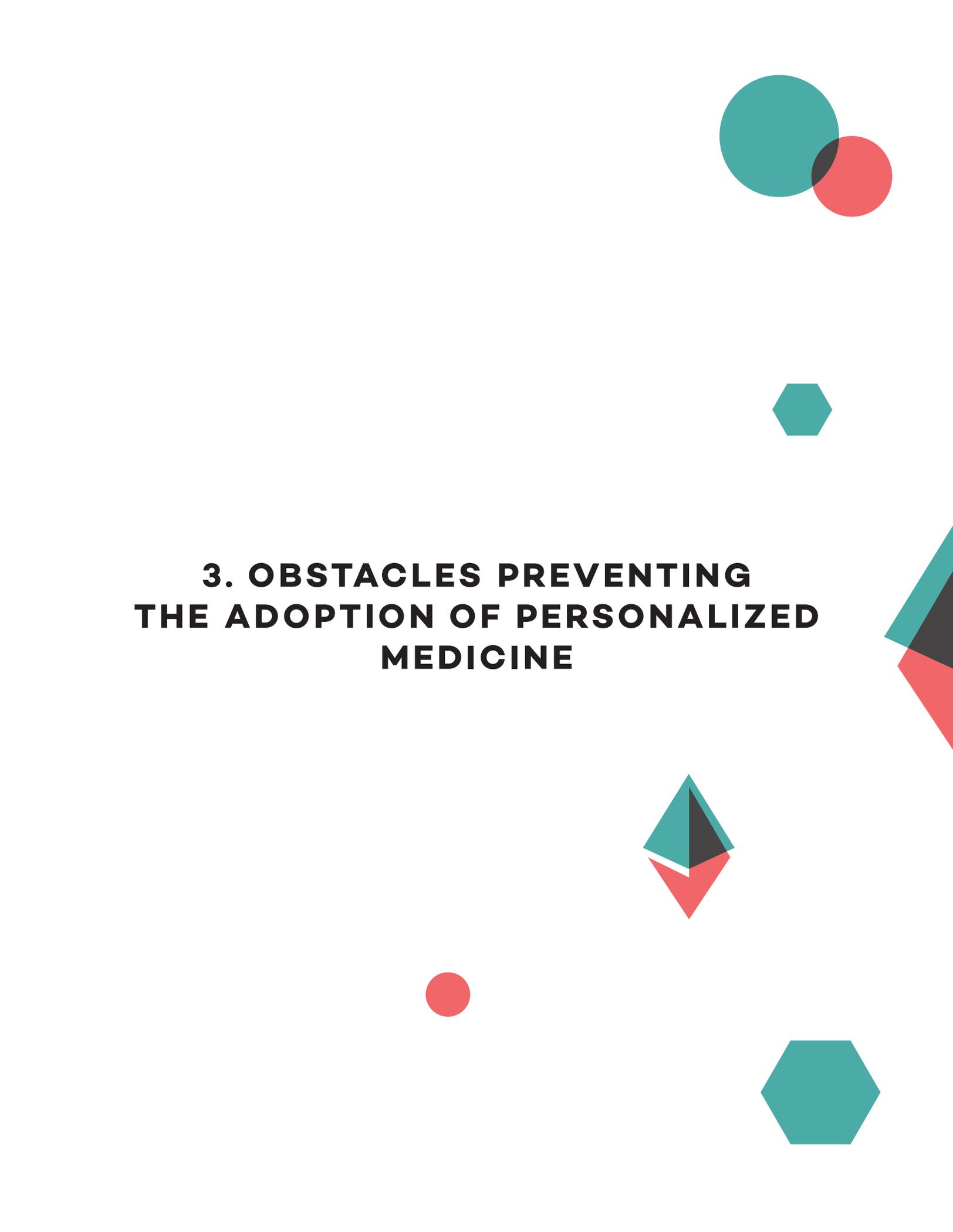
Personalized medicine is transforming healthcare by offering bespoke medical treatments catering to an individual's characteristics, needs, and preferences during all stages of care – including prevention, diagnosis, treatment, and follow-up.¹ The development of customizable treatment options has relied heavily on innovations in genomic medicine, which uses information from genomes and their derivatives to guide medical decision-making.² Accessing this type of genomic information has only recently become cost effective: The cost of sequencing the human genome, which initially took nearly 13 years and \$2.7 billion to complete, now approaches the price of a routine X-ray.³ Also, the digitalization of health data and recent widespread adoption of electronic medical record systems has made it possible to store and transmit genomic data en masse.⁴⁻⁶ This has led to a paradigm shift in medicine away from the classical approach of diagnosing and treating patients based on signs and symptoms, towards targeting treatment decisions using both an understanding of the genetic make-up of the disease affecting the patient, and the patient's individual genetics, epigenetics, biomarkers, phenotypes, microbiome, and overall health state.^{1,7,8}

The first wave of therapies targeted at specific molecules revolutionized oncology treatments starting in the early 2000s⁹⁻¹¹, following breakthrough research linking defects in protein kinases to the onset and progression of more than 400 diseases.¹²⁻¹⁴ This research directly led to the approval of more than 30 kinase-targeted drugs. In the past, the vast majority of these treatments would not have been cost effective to develop. However, further research and clinical trials have become cost effective for a larger proportion of these therapies through the use of validated biomarkers. This method reduces development costs by targeting clinical trial enrollment to candidates who are genetically predisposed to respond to the treatment, reducing unnecessary trial recruitment expenditures and improving the chance of drug approval.¹⁵⁻¹⁶

There are several ongoing personalized medicine projects that seek to leverage these new understandings of disease mechanisms to tailor patient treatments. The 100,000 Genomes Project is a ground-breaking genomics project launched by the UK government in 2012 that aims to sequence the genomes of approximately 100,000 individuals in the UK. A key objective of the project is to use genomics and other health data to help providers determine care plans.¹⁷ Recent efforts like iTARGET autism¹⁸ target specific conditions. Translating this research into personalized medicine will further require that providers across the continuum of care have timely access to these data in order to target care appropriately.

HEALTHCARE DELIVERY MODELS





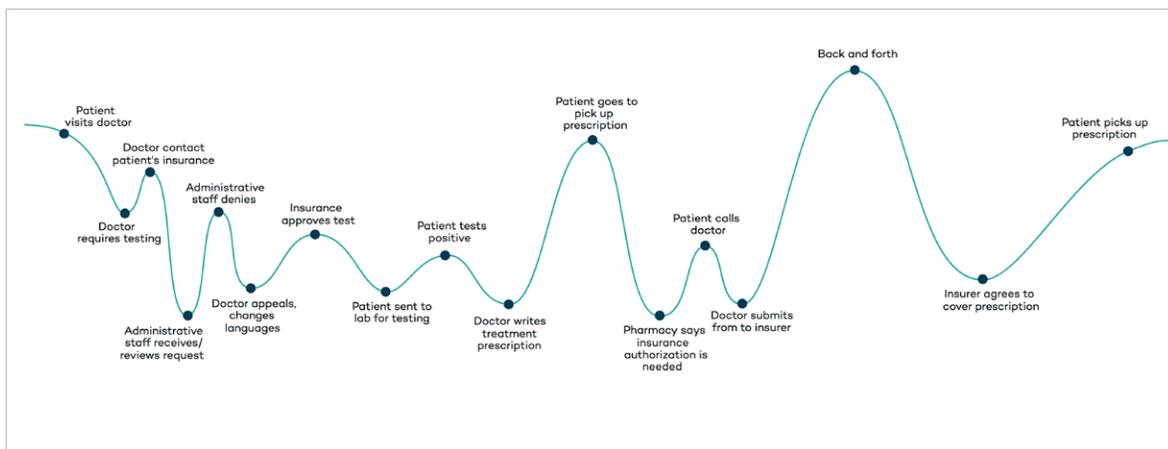
3. OBSTACLES PREVENTING THE ADOPTION OF PERSONALIZED MEDICINE

3.1 Current Data Exchange and Care Coordination Challenges

Despite the widespread digitalization of health records, the adoption of personalized medicine has been slowed by a lack of data exchange. The development of data formats and storage systems to date has been sporadic and ad hoc. As a result, healthcare organizations often maintain numerous non-compatible data structures that limit data sharing even within the organization, and pose significant problems for communication between entities. Data communication between healthcare providers is so limited that almost a third of patients report having to physically bring their medical records from one provider to another.¹⁹ Those that do not physically carry their records often have to arrange for them to be faxed between providers. Each year massive amounts of unstructured data – including billions of faxes – are transmitted in the US healthcare system.²⁰ Because these antiquated data are so difficult to synthesize, more than half of patients report that their medical record is incomplete despite attempts to share information.¹⁹ The lack of effective information sharing technology leads to substantial inefficiencies and information gaps.²¹ Even when information is shared, providers lack the infrastructure to effectively integrate, mine, and analyze the data.²²

Poor data exchange greatly limits coordination of care despite providers' best efforts, causing them to spend a disproportionate amount of time on administrative tasks. Physicians report spending almost half of their time processing documents, tracking down missing information, and filling out forms.²³ Almost a fifth of the time, primary care physicians (PCPs) report not receiving the result of a lab test they ordered ahead of a follow-up visit.²⁴ When specialists receive a patient referred from a PCP, almost half of the time they report not having received all the information they need on the patient ahead of their initial consultation; likewise, PCPs often do not receive information on their patients following a specialist visit.²⁵ The absence of data is particularly alarming in the context of emergency medicine: In almost a third of emergency department visits, the provider had no access to the patient's health records at the time of care.²⁶

THE CURRENT PATIENT JOURNEY



Deficits in communication and information sharing also have important implications for the continuity of care. Hospital physicians and PCPs rarely communicate directly; only about 34% of PCPs receive a discharge summary from a hospital prior to the first post-discharge visit.²⁷ Even when discharge summaries are received, they often lack important information on diagnostic test results, medications administered, and follow-up plans.²⁷

A lack of care coordination and issues with maintaining the continuum of care lead to redundant and avoidable financial expenditures. A study by Berwick and Hackbarth estimated that as much as \$1.3 trillion of annual healthcare spending in the US may be categorized as either wasteful or of no value to patients and was incurred due to failures in care delivery or care coordination, over treatment, administrative complexity, pricing failures, and fraud and abuse.²⁸ The process for prior authorization requests exemplifies the inefficient spending in the current healthcare system. Payers (insurance companies) often require providers to seek their authorization before administering certain high cost treatments. In the current system, providers must complete the applicable prior authorization form, and fax it to the payer. Payers then manually review the form and decide whether to approve, deny, or request additional information. While this reduces some unnecessary treatment, payers and providers end up spending between \$23 and \$31 billion each year processing prior authorizations²⁹. Unfortunately, while it is relatively easy to identify issues in the healthcare system, it has proven much trickier to find viable solutions. A Harvard Business Review report estimated that even if all currently assessed cost savings measures were implemented, only about \$400 billion of the potential \$1.3 trillion in savings would be captured.³⁰

3.2 Challenges to the Development of Targeted Treatments

The development of new therapies often takes more than a decade and costs billions of dollars.³¹ Only about 10% of treatments under investigation complete preclinical assessments, and only 5% of treatments entering clinical development are ultimately approved by the US Food and Drug Administration (FDA).³² As such, pharmaceutical companies look for mechanisms to increase the likelihood of FDA approval for therapies first coming to market.^{32,33} Companies also seek to maximize the utility of therapies that have already undergone pharmacokinetic and safety testing, primarily by investigating the potential for expanded label indications. While both of these processes lead to some expense savings, they remain arduous and costly within the current system.

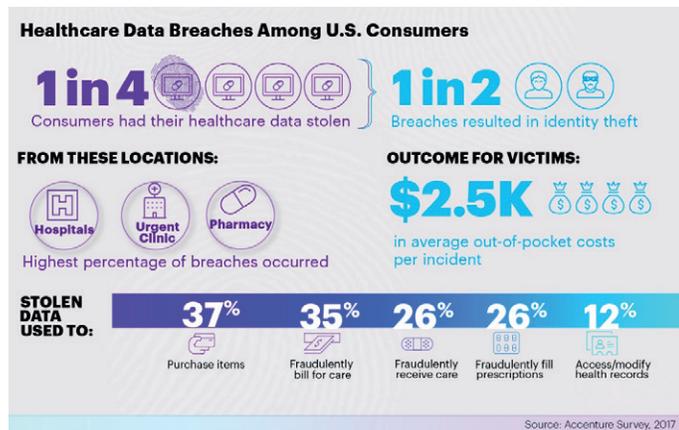
While hundreds of promising potential treatments have been identified, few treatments have been approved due in part to difficulties recruiting appropriate trial candidates. Current clinical trial recruitment strategies are slow and failure prone.³⁴ Recruiting through mass media marketing tends to be overly broad, resulting in numerous responses, but a low proportion of eligible participants, while recruiting through physician referrals results in a higher proportion of eligible respondents, but rarely amasses sufficient patients for a trial. With per-patient clinical trial costs totaling approximately \$40,000³⁵ and recruitment periods averaging 30 months³⁶, pharmaceutical companies often only fund clinical trials for the few treatments that have already demonstrated a high likelihood of success. Even when a trial is funded, a recent study found that 19% of all trials close because they fail to recruit sufficient patients.³⁴

Because clinical trials are so costly and time intensive, pharmaceutical companies often prefer to conduct retrospective analyses of their treatment to assess off-label effectiveness and identify potential target disease areas before committing resources to a trial.³⁷⁻⁴² Unfortunately, there are not many existing large, generalizable databases that contain detailed genomic data with which to do this research. The databases that are available often lack the full information needed to accurately conduct effective retrospective analyses. Insurance claims databases – which are the most widely available large datasets – do not collect the necessary lab and genomic data. Meanwhile, the electronic medical record databases that do include this genetic data tend to not aggregate sufficient sample sizes – especially within specific disease subpopulations – to be statistically meaningful. Additionally, companies often must pay large licensing fees to contract an entire database of patient records in order to access a small sample of applicable data.

3.3 Current Security and Privacy Challenges

The existing healthcare system has failed to deliver the data security and privacy required to drive the widespread adoption of personalized medicine. Due to its sensitivity, healthcare data is strictly regulated. Both the US, through the Health Insurance Portability and Accountability Act (HIPAA), and the EU, with the General Data Protection Regulation (GDPR), have implemented stringent requirements for safeguarding healthcare data and levee large fines on companies that fail to meet those requirements.^{43,44} Despite these regulations, entities rarely encrypt their private databases due to the costs and data exchange issues associated with encrypted data. The lack of security has led to periodic, large scale data breaches⁴⁵, the largest of which exposed the names, birth dates, Social Security numbers, and home addresses of 79 million Americans⁴⁶. Despite these security vulnerabilities, patients have had little say over who stores their data and how it is used.

A study published in the Journal of Personalized Medicine found that 71% of Americans are concerned about genetic information storage and privacy³, highlighting the need to have secure systems in place to protect the confidentiality of genomic information. Maintaining the confidentiality of genomic data is difficult, however, because even if a specific gene is concealed, other markers around a concealed gene can indirectly identify it.¹ Inappropriate sharing of genetic data can also reveal sensitive information about an individual's closely-related family members. Furthermore, even if genomic data is not currently identifiable, advances in research techniques risk the exposure of sensitive information in the future, unless steps are taken to protect it. The advent of personalized medicine requires advanced data security measures that are strong enough to guard records against attackers and nimble enough to protect genomic data, yet still sufficiently flexible to permit the flow of information required to ensure continuity of care.

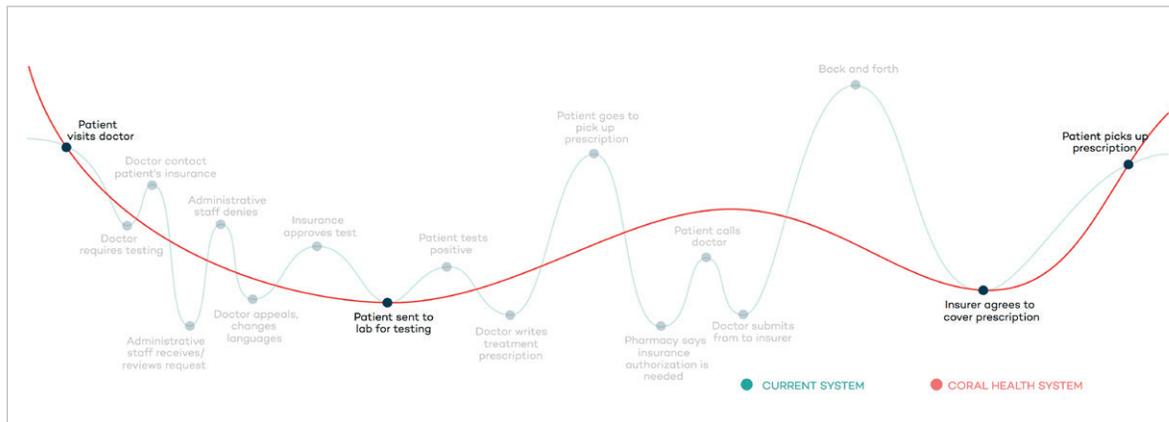




4. CORAL HEALTH: THE BLOCKCHAIN FOR PERSONALIZED MEDICINE

Coral Health will leverage blockchain technology to create an accessible, secure, and scalable healthcare ecosystem that will address many of the current problems facing the industry, and power the widespread adoption of personalized medicine. Patients and other stakeholders will interact with the Coral Health ecosystem using customizable apps initiated by Coral Health and tokenized for further development. With these tools, stakeholders will be able to secure, share and digest data as well as build powerful functionality that will streamline care and reduce administrative tasks.

THE PATIENT JOURNEY REIMAGINED



4.1 How Coral Health Ensures Data Security

Two key features of the Ethereum blockchain ensure the security of data stored in the Coral Health ecosystem: the use of a distributed network of storage nodes, which prevents any one entity from having exclusive ownership of all data, and the use of an immutable ledger that tracks all transactions and records, preventing mistakes such as double payment or other retroactive attempts to alter records. To further supplement these safeguards, Coral Health will fully encrypt all data, using modern techniques that deliver full HIPAA and GDPR compliance to anyone utilizing the Coral Health network.

Blockchain's peer-to-peer distributed ledger technology allows information to be shared amongst peers but not copied by them; furthermore, data from each node is available to all others on the network.⁴⁷ Thus any person or organization that uploads data to the Coral Health ecosystem is always assured access to their information. Stakeholders will no longer have to trust a third-party to safeguard their data against outages or other interference that may prevent access.

Coral Health's blockchain system will track all transactions that occur on the network in blocks that are added to the ledger in chronological order. After a new transaction is entered into the database and subsequently verified, the records cannot be changed except with the permission of the owner, thus ensuring sensitive medical records cannot be altered either by outside attackers or by accidental mishandling. Additionally, financial transactions will be embedded in smart contracts which automate collection and verification, alleviating many common payment processing concerns, such as double payment and slow collection times.

In the current healthcare system, medical records are often stored unencrypted on Oracle servers, making HIPAA and GDPR compliance a cumbersome burden for entities that need to access and transfer that data. However, with the Coral Health system, all data will automatically be encrypted to a standard that surpasses current government standards when it is uploaded to the network, making data-security compliance easy for anyone that chooses to use the Coral Health ecosystem.

4.2 How Coral Health Ensures Data Privacy

Patients who use the Coral Health platform maintain complete control over the privacy of their own health records through the use of smart contracts. These customizable contracts programmed on the Ethereum blockchain will allow patients – and those tasked with safeguarding patients' records – to set precise parameters on access to a patient's health record, both in terms of which information is shared and the duration for which the records can be accessed.

For example, a patient and/or his/her PCP would be able to grant a lab access to the patient's basic characteristics (age, gender, race) before a HbA1c test, but restrict access to sensitive genomic information and medical record that is not relevant to the current procedure; access could then be programmatically revoked following the lab visit. Conditional rules for data access can also be established via smart contracts, allowing for further flexibility without compromising privacy.

Smart contracts will also enable patients to delegate control of their medical records to their PCP or other trusted provider, should the patient prefer assistance in transferring information between different specialists, payers, and other stakeholders.

Coral Health's patient-driven record governance design simplifies compliance with HIPAA and GDPR regulations, which stipulate that patients must consent to any disclosure of their private health information and that third parties must receive confirmation of consent from patients before accessing their data.^{43,44} Smart contracts ensure that these requirements are automatically met when data is accessed.

In addition to providing privacy and simplifying regulatory compliance, smart record permissioning addresses many of the ethical concerns raised with personalized medicine. Over half of physicians report that in the event of a patient testing positive for Huntington's Disease, they would tell the patient's relatives of their risk of Huntington's Disease against the patient's wishes.³ By putting control of data in the hands of the patient and requiring patient approval before third parties can access patient records, stakeholders will be shielded from the complex ethical considerations that accompany having unrestricted access to data. Likewise, the ethical questions of what mutations a genomicist must scan for or discuss with a patient do not arise if genomic data is stored with the patient and not the genomicist by default.⁴⁸

4.3 How Coral Health Provides Streamlined and Secure Data Exchange

The Coral Health ecosystem enables anyone in the healthcare system to seamlessly upload and share their data to a single, integrated network. Data storage on the Coral Health network is centralized in the sense that all data is encrypted and stored on the same ledger, but decentralized in that there are thousands, potentially millions of nodes that store their own portions of this ledger. This structure not only guarantees entities access to their own data, but will allow participants to read other's data. For example, whenever a healthcare entity creates a medical record (e.g., prescription, lab test, pathology result, MRI), the information is immediately added to the blockchain and each person authorized to read this data will have the same, constantly updated view of the information, allowing for real-time, streamlined decision making.

Coral Health's initial data functionality will include applications that allow clients to upload common data types as well as customizable tools that clients can use to handle more complex data. In addition, Coral Health's unique flexible data structure ensures that the network will be able to continually adapt to accommodate all types of health records, present and future. Please see section 6.5 for a complete description of Coral Health's data storage methodology.

4.4 How Coral Health Provides a Secure Method to Aggregate Metadata

All data entered into the Coral Health system will be uploaded with key metadata that will allow participants – such as health authorities and genomics researchers – to perform informative research at the aggregate level, but will not reveal any identifying information on an individual basis. For example, when a lab writes the results of a patient's test for HER2 breast cancer to the Coral Health network, the metadata uploaded along with the record will show that a patient was tested for HER2 breast cancer, but will not show the lab result or any information that could be used to identify the patient. By aggregating this metadata, Coral Health enables third parties to broadly search the network for specific patient groups, such as the number of patients who were tested for HER2 breast cancer; then, if the exploration of the metadata proves promising, the interested party can request additional data from those patients. Once a researcher has received decryption access to the data they need, aggregating and analyzing that data is trivial, as all data received through the Coral Health network is stored in standardized digestible formats.

Coral Health's tokenized permission approach to data access guarantees that stakeholders looking to conduct research have access to the level of data they need, and also ensures that they do not have to pay for excess data. For example, researchers that only need to request access to anonymized, aggregate data would not have to offer as large of a token incentive to encourage patients to participate as a researcher that required patient-identifiable information would have to offer. Coral Health's incentivized permission system thus lowers barriers to research by eliminating the excess data acquisition costs typically associated with current databases.

4.5 Benefits to Patients

Coral Health will fundamentally simplify patient interactions with the healthcare system. By storing their records on the Coral Health network, patients will no longer have to physically carry their own data from one provider to another, or fill out the same redundant paperwork each time they visit a new provider. Patients will also receive prior authorizations from their insurance company in real-time, giving patients assurance about what treatments will be covered by their insurance before they leave their provider's office.

The Coral Health ecosystem will also provide patients with better care coordination and relink the continuum of care by granting all providers the same access to patients' records, regardless of their network affiliation or place of service. When a patient visits an emergency department, for example, the providers on staff can be granted visibility into that patient's medical history, reducing the risk of inappropriate or ineffective care. Likewise, when a patient is discharged from a hospital, the patient's PCP will have timely access to discharge records, preventing any double work or delays in follow-up care. These efficiencies will reduce redundant testing, ineffective treatments, and cumbersome administrative tasks, leading to substantial savings that could be passed along to patients in lowered premiums.

Prior studies have found that patients respond positively when given open access to their medical records.^{49,50} In order to achieve patient buy-in, Coral Health plans to test pilot applications with patient focus groups in order to develop functionality that patients find reliable and trustworthy. Coral Health will then run physician workshops to engage physicians and make sure they can serve as an effective resource to answer their patients' questions about the technology. Lastly, Coral Health will lead extensive patient education efforts to communicate the numerous benefits of Coral Health and demonstrate to patients the control they could have over their data and privacy. For patients who, despite these efforts, still do not consent to participate in the Coral Health network, an opt-out model similar to that proposed by Roden et al.⁵¹, will be implemented.

4.6 Benefits to Providers and Medical Groups

With Coral Health, providers will significantly reduce time wasted on document processing and free themselves to focus on delivering better care. Coral Health makes data exchange simple and efficient by automatically synthesizing a wide variety of data types. Smart contracts can then programmatically process large amounts of the data that providers currently process manually. Without barriers preventing the exchange of data, physicians will be able to better coordinate care with other providers and determine how best to treat their patients within the context of the broader continuum of care.

The Coral Health system will drive significant time savings for providers by reducing administrative communications with payers. Providers and their staffs spend large amounts of time checking insurance eligibility, preparing prior authorizations, and submitting medical claims.^{23,52,53} A significant portion of this time is spent appealing insurance denials and responding to requests for further documentation. Since Coral Health enables medical groups to automatically grant payers read access to the data they need, payers will be able to apply smart contract rules to determine procedure eligibility and verify services rendered automatically. With this seamless data exchange, the laborious back and forth between payers and providers is dramatically reduced.

This gives providers more time to focus on clinical care; it also speeds up claim processing times, allowing payers to immediately reimburse providers for their services.

Coral Health plans to drive provider adoption by highlighting the significant administrative improvements it affords and incentivizing data sharing. Coral Health will lead focus groups and physician outreach efforts to demonstrate how much time participants can save by using Coral Health to handle data exchange and interactions with payers. Furthermore, Coral Health will tokenize data exchange to compensate providers who share their data. By tokenizing data exchange, Coral Health will encourage providers to start treating data as a revenue driver instead of an asset that should be guarded. As the Coral Health network grows and patients regain control over their health data, providers will remain a critical resource for patients, helping them delegate and manage data access.

4.7 Benefits to Payers (Insurance Companies)

Coral Health provides payers with the capability to automate a diverse array of administrative tasks. With Coral Health, payers will be able to program their eligibility and reimbursement rules to interact with the Coral Health network using smart contracts. By accessing applicable patient data stored on the blockchain, smart contracts will be able to efficiently perform administrative tasks, such as prior authorizations and claims processing, that are often processed manually. For example, to process prior authorizations, smart contracts would reference the applicable patient data and determine patient eligibility in real-time. Because Coral Health's network is designed to handle a wide array of common data types, automated prior authorization functionality can process all types of prior authorization requests, including prescriptions, lab and genetic tests, and surgeries.

Likewise, claim processing will be automated by integrating reimbursement rules into smart contracts. The smart contracts will reference the services patients received, locate the reimbursement rates for the specific service and provider, and automatically approve the appropriate payment amount. Because all services are cryptographically verified prior to be added to the central ledger, Coral Health greatly reduces the amount of auditing payers have to do when reviewing claims.

Coral Health proposes to drive payer adoption of its ecosystem by holding prototype reviews and workshops with insurance companies to explain the operational efficiencies/cost savings they can realize by participating in the ecosystem.

4.8 Benefits to Pharmaceutical Companies

The Coral Health ecosystem will benefit pharmaceutical companies both through improvements to the treatment study process and through reducing administrative burdens.

Coral Health's secure and centralized data storage system will reduce clinical trial recruitment costs and allow pharmaceutical companies to efficiently evaluate the safety and efficacy of their existing treatments. Pharmaceutical companies will be able to search the metadata stored on the Coral Health blockchain to assess potential sample sizes for an upcoming trial. If the sample sizes look promising, pharmaceutical companies could then request read access to the applicable patient records and invite interested patients to enroll in the trial.

Pharmaceutical companies will also be able to use the data stored in the Coral Health ecosystem to conduct retrospective analyses. Searchable metadata will allow pharmaceutical companies to contact the patients who are most likely to have taken their medication, and recruit these individuals for participation in a study. Access to the full medical records of patients who chose to participate in the study would allow pharmaceutical companies to more effectively study the success of their treatments and better identify promising patient subpopulations for expanded indications.

Access to study participants' full medical histories also provides a cost-effective way to study the long-term effects of treatments. The FDA often requires long-term assessments of treatment for chronic conditions; however, meeting this requirement currently requires running expensive clinical trials, since existing insurance claims and electronic health records databases often lack sufficient follow-up information or are missing records of patient health outcomes.

Participating in the Coral Health ecosystem will also substantially reduce administrative costs for pharmaceutical companies by automating compliance reporting. The FDA Adverse Event Reporting System (FAERS) requires that drug manufacturers send any adverse events reported to them by healthcare professionals or consumers to the FDA.⁵⁴ Currently this compliance reporting requires costly manual report generation. With the Coral Health ecosystem, pharmaceutical companies could incentivize providers and consumers to upload reports of adverse events to the blockchain. Smart contracts would then automatically generate reports of events and securely deliver them to the FDA.

Likewise, pharmaceutical companies could use Coral Health's smart contract functionality to better manage clinical trial adverse event reporting; any adverse events that occurred could be programmatically identified, processed, and sent to the institutional review boards (IRBs) overseeing a trial site. This would save pharmaceutical companies administrative costs spent on compliance reporting. It could also improve the quality of the information the IRB receives, potentially increasing the safety of future clinical trials.⁵⁵

4.9 Benefits to Public Institutions and Researchers

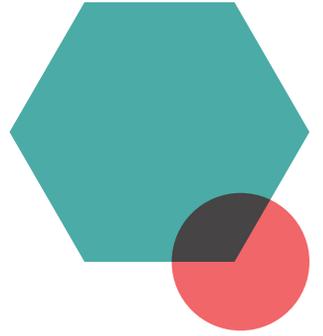
The Coral Health ecosystem could dramatically improve disease surveillance and monitoring by providing real-time alerts on potential disease trends and outbreaks. Currently, public health authorities, such as the Centers for Disease Control and Prevention (CDC), spend significant time and money setting up intricate data sharing agreements with other public health authorities, clinical laboratories, and physician offices just to aggregate enough data to comment on disease trends.^{56,57}

This design entails substantial setup costs and ongoing work to synthesize and aggregate data coming in from the hundreds of distinct sources, severely limiting the number of diseases public health authorities can effectively monitor. Moreover, manually reporting data leads to significant lags that limit the ability to identify and treat outbreaks as they occur.

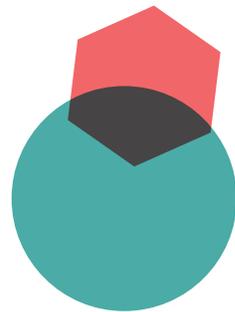
Using Coral Health, health authorities will be able to request decryption privileges from patients so that they can use completely anonymized versions of patients' full health records to monitor disease trends in real-time. Public health authorities will also have the ability to program smart contracts to aggregate anonymized data and create disease reports, monitor trends, and identify potential outbreaks. If a potential outbreak is identified, the public health authority will already know the scale of the outbreak and can implement measures to address the outbreak before it spreads.

Coral Health's network can also serve as a genomic data repository to further scientific discovery. Patient genomic data from disparate studies can be linked by securely sharing access to the data on Coral Health's network, reducing the amount of redundant genome sequencing across studies. This will free up funds for new research, accelerate our understanding of the human genome, and drive further diagnostic and therapeutic discovery.

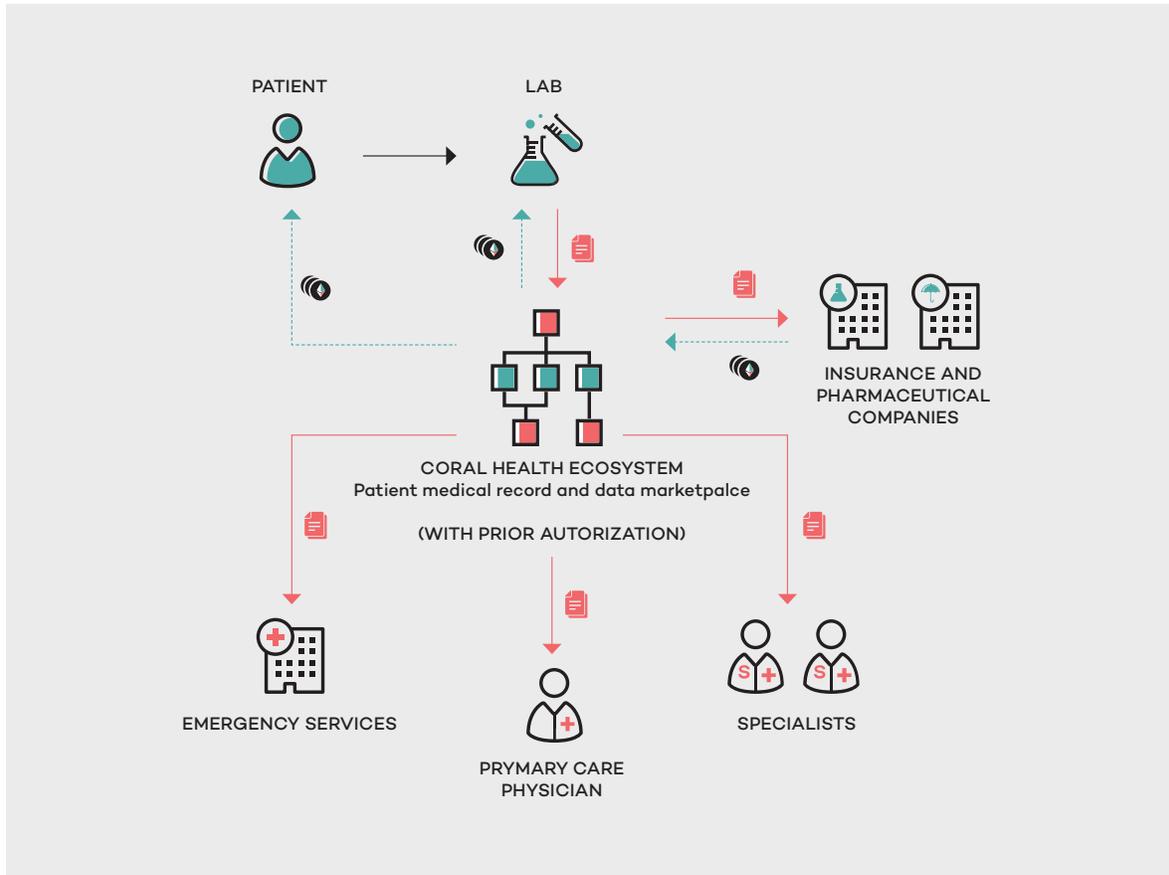
Once a critical mass of participants has been reached, Coral Health will demonstrate the data storage, reporting, and monitoring strengths of the Coral Health system to interested public health authorities. To facilitate participation, Coral Health will offer seed tokens and training to the public entities that choose to participate, and will assist partners with smart contract programming and data interpretation, as needed.



5. USE CASES



5.1 Sharing Lab Results



GOAL

To eliminate data silos by allowing labs, physicians, hospitals, and other stakeholders to easily access and share a patient's medical data.

EXAMPLE USE CASE

A patient visits a lab for a blood test. Once the lab has processed the sample, the patient receives a notification that the results of the test are available, and can choose whether to allow the lab to encrypt the data with her public key and post it to the Coral Health platform. The patient grants permission for the data to be posted, and also grants permission for her health care providers to access the data. Future retrieval of data is now streamlined: If a patient arrives in an emergency room and is unresponsive, the emergency room can quickly access her medical records through Coral Health and thus provide swift and personalized treatment.

INCENTIVES

By allowing her medical records to be posted to Coral Health, a patient avoids having to transport lab results himself or having to arrange for records to be faxed to various caretakers. He also ensures that all of his medical providers have the information necessary to provide the best care possible. Labs reduce the administrative costs of having to print and mail, or fax each test result to individual providers. Additionally, labs and patients gain access to the Coral Health ecosystem, where they may receive payments from insurance firms that consult the uploaded data to process claims or from pharmaceutical companies that select the data for use in studies. Doctors and hospitals receive access to centralized medical data on their patients at no cost, reducing administrative labor and expenses. In the adoption stage, patients will initially be gifted a small amount of Coral Health tokens for uploading a specified set of medical records. Beyond the small onboarding amount, a patient can further earn tokens per Sections 5.3 and 5.4.

INITIAL IMPLEMENTATION

Currently, Coral Health is in active discussions with a large lab network to begin writing patient data to the platform for selected blood tests.

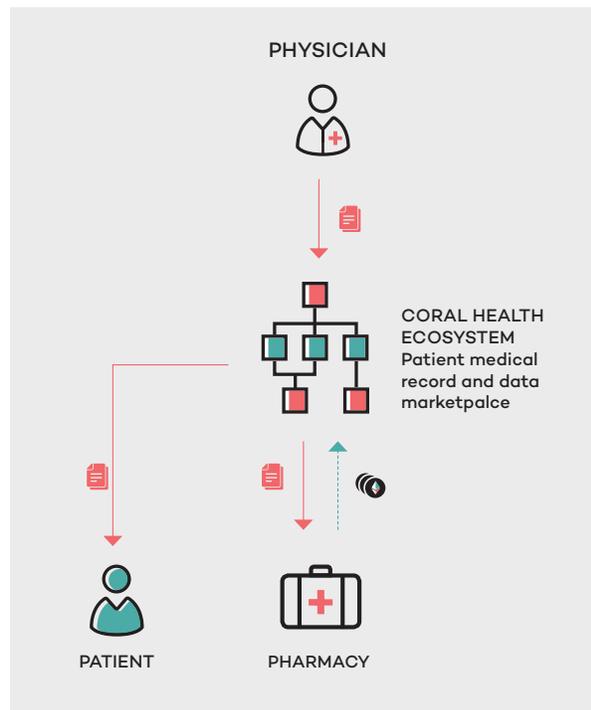
5.2 Streamlining the Prescription Filling Process

GOAL

To streamline the prescription filling process by speeding up fill time, reducing misinterpretation of physician orders, and eliminating fraud.

EXAMPLE USE CASE

A physician writes a prescription order for a patient and posts the order to the Coral Health platform. To fill the prescription, the patient either provides his public key to a pharmacy of his choice or delegates this task to his physician through use of a smart contract. The pharmacy then pays a fee to Coral Health in order to access the records on the blockchain, and uses the patient's public key to retrieve and verify the patient's prescription order. Lastly, the pharmacy fills and dispenses the prescription.



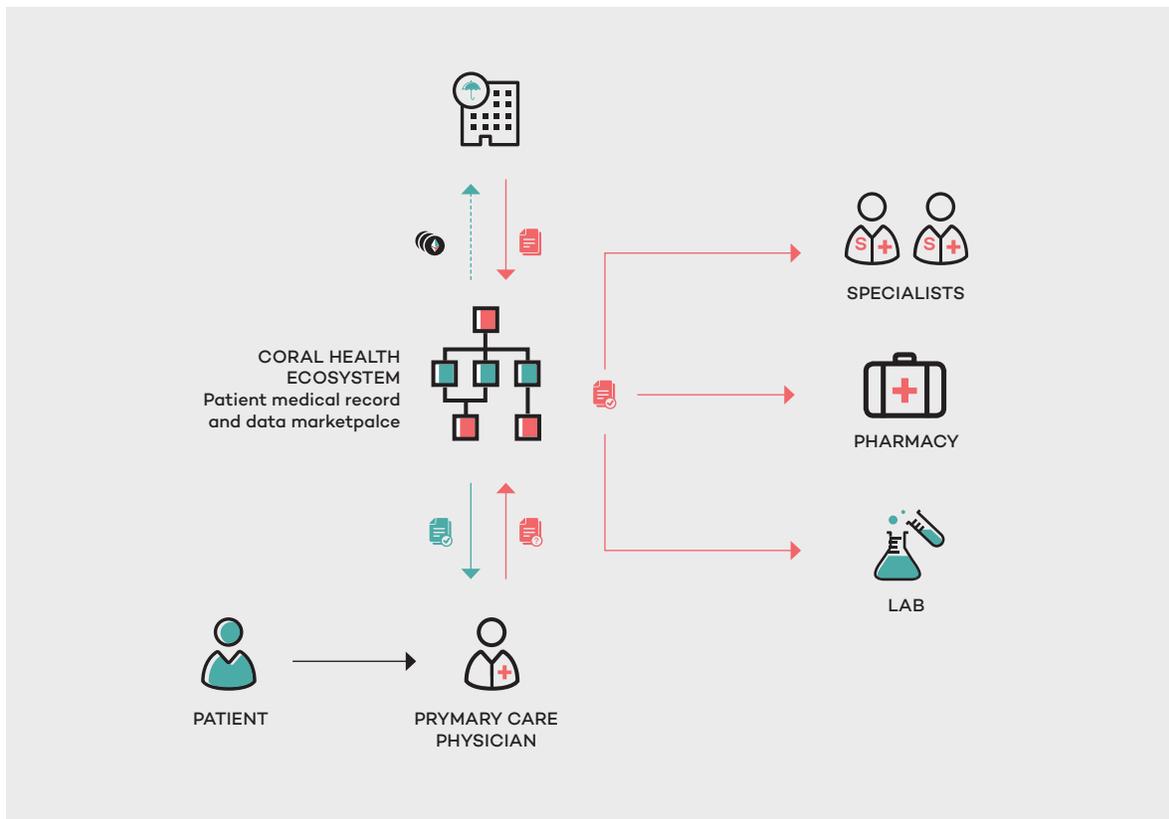
INCENTIVES

Pharmacy employees currently receive and verify prescription orders manually. Automating these processes will result in significant cost savings for pharmacies that elect to access prescription records through the Coral Health platform. Physicians reduce the time spent correcting misinterpretations, clarifying prescriptions orders, or otherwise communicating with pharmacies following a patient's visit. Patients, meanwhile, gain flexibility by no longer having to designate a pharmacy to receive the prescription at the time of their physician visit, keep track of a written prescription, or otherwise coordinate prescription fulfillment between physicians and pharmacies.

INITIAL IMPLEMENTATION

Coral Health is discussions with pharmacies and big-box providers to pilot the prescription retrieval process, and will encourage pilot partners to compare the order accuracy and dispensing speed achieved with the Coral Health system to that of their existing manual processes. A small amount of Coral Health tokens will be gifted to the pilot providers and pharmacies initially as part of their onboarding process. Coral Health will broaden the trial network after a successful process has been implemented with the pilot group.

5.3 Automated Execution of Insurance Prior Authorization



GOAL

To reduce – and eventually eliminate – the error-laden human effort of manually reviewing and replying to prior authorization requests, and to reduce appeals caused by incorrect interpretation of manually written prior authorization forms.

EXAMPLE USE CASE

Insurance companies write smart contracts to the blockchain that contain the policies used to determine authorization. A provider then submits a prior authorization request for a specialist visit, procedure, or prescription to the blockchain. The payer's medical policy smart contract automatically determines authorization using the patient's medical information stored in the Coral Health ecosystem and the information in the request. Authorization information is then immediately relayed back to the provider. The patient – as well as any labs, pharmacies, specialists, and other stakeholders to whom the patient had delegated access – would also be able to verify insurance authorization in real time. The insurance company pays a fee to the Coral Health system, portions of which are paid to the patient and lab to encourage continued participation in the system, for each authorization claim processed through the blockchain.

INCENTIVES

The automated prior authorization process will result in significant cost savings for payers, which currently spend substantial sums to evaluate and respond to requests manually. Doctors will be able to proceed with care immediately instead of having to put their patient's care on hold while waiting for a response from the payer. Patients, meanwhile, will be saved the worry of wondering whether the procedure recommended by their provider will be covered by their insurance. With prior authorization information immediately available, doctors and patients together can confidently proceed with a care plan specifically tailored to the patient's needs and applicable insurance coverage.

INITIAL IMPLEMENTATION

Coral Health is working with vendors of payer data to establish partnerships with a select group of insurance companies, and will pilot the automated authorization process for a small set of medical procedures with these partners. To encourage participation, Coral Health will provide pre-written authorization contracts for these pilot procedures; for example, Coral Health will prepare a smart contract that approves mastectomies for patients whose lab results show BRCA1/BRCA2 gene mutations. Coral Health encourages payers to employ both automated and manual efforts concurrently during the trial period; this approach will allow a direct comparison between the two systems and thus better demonstrate the improved speed and accuracy of Coral Health's automated process.

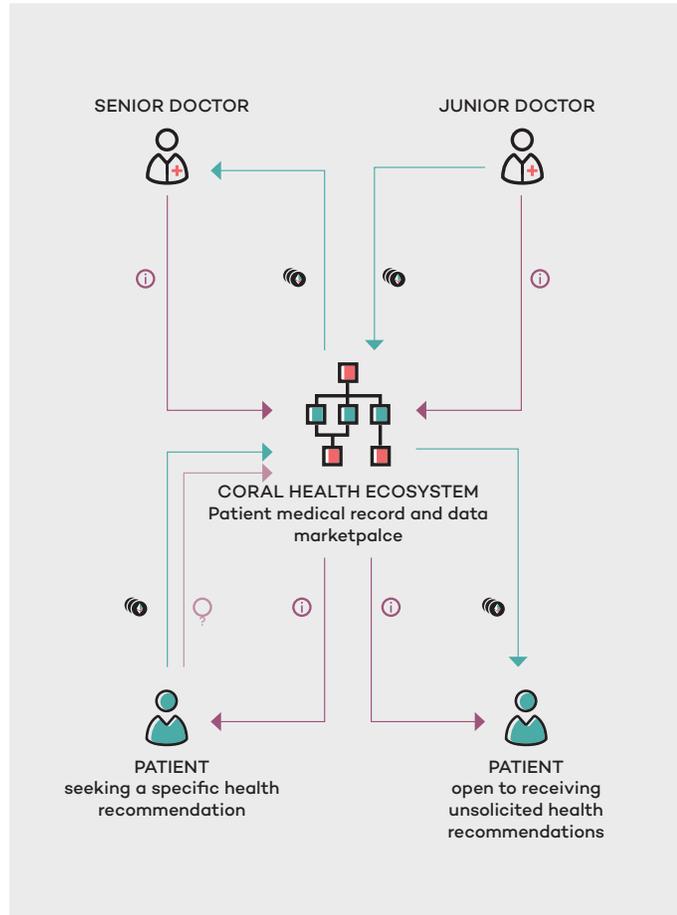
5.4 Enabling Communication between Patients and Providers

GOAL

To match individual patients who want customized health tips with doctors who are interested in providing them. Such a market will allow patients to receive customized health recommendations from specialists in different fields, and will facilitate the matching of patients and specialists based on the patient's characteristics and medical history.

EXAMPLE USE CASE 1

A patient submits a request for a health recommendation or comment regarding a specific complaint or ailment. The Coral Health system automatically sends this request to participating physicians in the relevant field. A physician accepts the request and responds with a recommendation; the system then processes the payment from the patient, issuing a fee to the responding doctor.



EXAMPLE USE CASE 2

A patient indicates through the Coral Health patient interface that he would welcome health tips from specialists in any field. A junior doctor, looking to grow her business, reviews the records of patients in her area who are open to receiving unsolicited recommendations, searching for cases in which her expertise may be relevant. The junior doctor selects a patient, and pays a fee in order to contact the patient with a relevant health tip. The patient receives the personalized recommendation from the specialist, and is connected with a potential healthcare provider.

INCENTIVES

Patients seeking health information about a specific topic receive a recommendation that is far more personalized than those provided by a web search. Senior doctors gain a new way to monetize their expertise, without having to overbook their schedules, while junior doctors can access a new market of potential patients, and build their brand within their specialty. Payments incentivize patients to allow junior doctors to contact them with recommendations.

INITIAL IMPLEMENTATION

Many public health authorities fund initiatives that connect their patients with providers. Coral Health is currently in discussions with a public health authority regarding the launch of a pilot program that would link its patients with physicians interested in participating in the trial.

5.5 Clinical Trial Recruitment

GOAL

To provide pharmaceutical and medical device companies with a quicker and more cost-effective alternative to current clinical trial recruitment, which often involves significant expenditures in order to purchase patient contact information from independent data vendors and to mount extensive pull-marketing campaigns.

EXAMPLE USE CASE

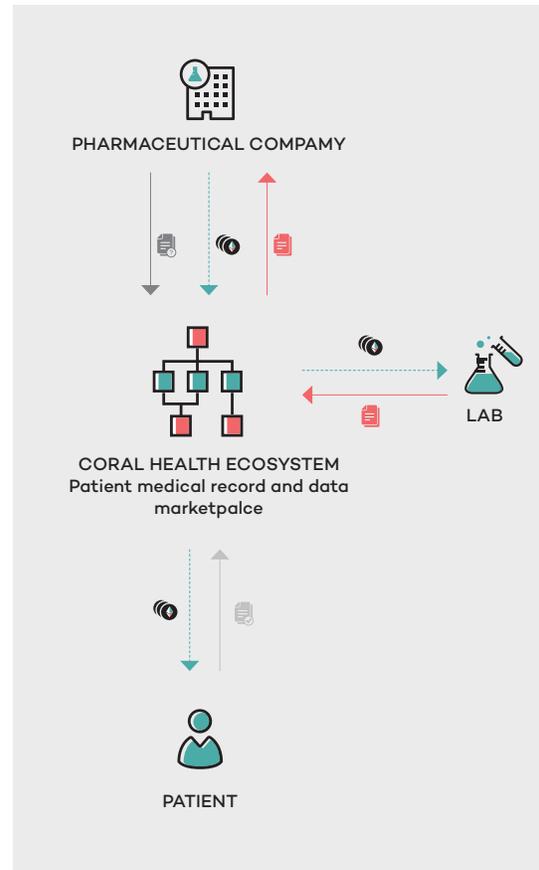
A pharmaceutical company searches metadata stored on the Coral Health blockchain to identify potential patients for clinical trial recruitment. The company then broadcasts a message to selected patients, which includes a request for read access to their medical records, including any relevant lab test results. If the patient grants access, Coral Health processes a payment from the pharmaceutical company, issuing part of the collected fee to the patient, and another portion to the labs that posted the patient's relevant test results.

INCENTIVES

Pharmaceutical and medical device companies would significantly reduce spending on data purchases and marketing efforts by directly targeting eligible patients. Patients, meanwhile, would gain access to new treatment options, in addition to receiving payments for participating in trials. Labs that participated by posting results would have a new way to monetize their data.

INITIAL IMPLEMENTATION

Once sufficient patient data is stored on the network, Coral Health will work with pharmaceutical and medical device companies to demonstrate the platform's strength as a clinical trial recruitment tool. Coral Health will also provide seed tokens to these companies in order to reduce the barrier to adoption.



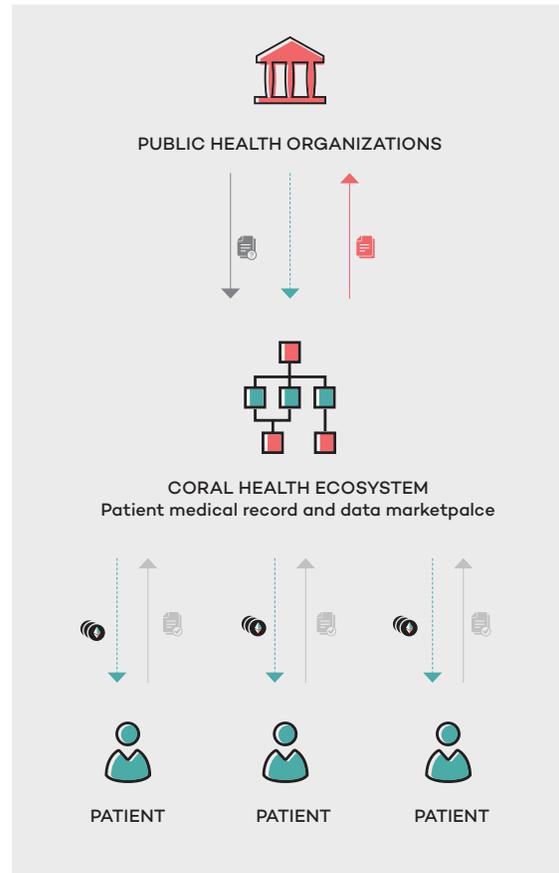
5.6 Facilitating Improved Public Health Initiatives

GOAL

Give public health authorities actionable, real time access to incidence, health outcome, and epidemiological data.

EXAMPLE USE CASE

Patients grant decryption privileges to their local health authority, allowing the health authority the ability to monitor anonymized versions of their full health records in real time. The health authority pays a fee to participating patients and begins monitoring the records. Subsequently, the authority notices an uptick in diagnoses and positive enzyme immunoassay results within a certain jurisdiction, indicating an increased incidence of Lyme disease in that area. The health authority can then take action to curtail the spread of the disease by informing the public of the presence of Lyme-carrying ticks in the area and taking steps to educate people in the prevention and detection of Lyme.

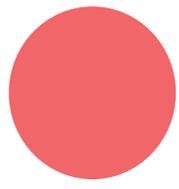


INCENTIVES

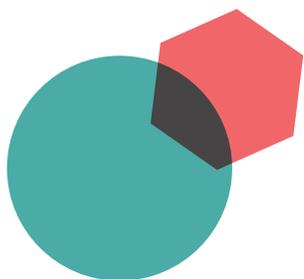
Public Health authorities will gain real time insight into disease incidence and outcomes within their jurisdiction, which will allow them to keep a close watch on potential concerns, and to take immediate, responsive action should a disease outbreak occur. Payments will incentivize patients to participate in the program.

INITIAL IMPLEMENTATION

As with pharmaceutical and medical device companies, Coral Health will work with health authorities to demonstrate the strengths of the system once a sufficient amount of patient data is collected. Coral Health will offer seed tokens and training to public entities that choose to participate, and will also provide data interpretation in order to assist the health authorities in drawing actionable insights. For an initial launch, Coral Health will approach the health authorities that have indicated interest in the patient-provider interaction program.



6. TECHNICAL IMPLEMENTATION



6.1 Overview

The Coral Health system has been conceived and developed on the Ethereum blockchain. It consists of two elements: a Coral Health token and the Coral Health Ledger Smart Contract. The token is the standard ERC20 token contract on the Ethereum blockchain, which will be used throughout the system to facilitate the necessary economic exchanges between users of the Coral Health system. The Coral Health Ledger Smart Contract, meanwhile, will implement a database of all records that have been uploaded to the network. The Ledger will store only minimal metadata about medical data records; actual records will be encrypted and stored off the blockchain, as described in the section below.

The Coral Health Ledger Smart Contract will also be extensible through the use of customizable data type contracts that may be published either by Coral Health or by third parties. These customizable and independent contracts will allow participating parties to control access to medical records by way of a delegation mechanism, in addition to facilitating a number of other functions.

In order to spur adoption, Coral Health will create canonical client applications that will allow patients and other stakeholders to interact with the Coral Health ecosystem. The Coral Health ecosystem will also allow external organizations to develop additional client applications specialized to their needs.

6.2 The Coral Health Ledger

The Coral Health Ledger Smart Contract is a contract on the Ethereum blockchain that is responsible for keeping a complete list of medical data files – as well as an access control list – using the following data structures.

```
struct Multihash {
    uint8    hashFunction
    uint8    size
    bytes32  hash
}
struct Record {
    address  patient;
    address  datatype;
    bytes16  year;
    bytes8   month;
    Multihash payload;
}
struct AccessControlListEntry {
    address  account;
    Multihash payload;
    bytes32  encryptedKey;
}
```

The data structures of the Coral Health Ledger Smart Contract are highly specialized to the data fields germane to raw healthcare data; data is not simply recorded in a string blob to be parsed later, but rather is pulled into defined structs that allow the data to be eminently digestible, and immediately usable by applications working in the Coral Health ecosystem. For example, results from a genetic test that were written to the Coral Health network could – without any further processing – be automatically referenced by a data type smart contract that would authorize insurance payment for the test.

6.3 Supported Data Types

Coral Health is envisioned as a scalable network that can accommodate all types of health records, present and future. The network must therefore allow for a wide variety of coexisting data types, and anticipate innovation in the healthcare space that will result in novel data types.

Coral Health will initially publish smart contracts for a number of common data types, such as genomic sequences, 2D or volumetric image data, medical questionnaires, and lab results. Participants – including medical labs, researchers, or manufacturers of new diagnostic tests – will also be able to publish customized smart contracts that cater to their own data needs. As the Coral Health system grows, data structures will continually be added to accommodate the disparate array of existing data types. Coral Health will work with labs, insurance companies, and other entities that join the system to standardize data output formats across healthcare fields.

The smart contracts developed for each data type would include API endpoints that both identify the contract and store additional public metadata specific to the type of data. Below is an example of the smart contract for a genetic test for breast cancer, as well as a list of initial standard data types for which Coral Health will develop smart contracts.

Example test:

```
struct IHCMetadata {
    bytes16    tumorSite;
    bytes16    specimenSite;
    bytes16    specimenCollectionYear;
    bytes8    specimenCollectionMonth;
}
function name() constant returns (string) {
    return "ImmunoHistoChemistry (IHC) version 1";
}
function url() constant returns (string) {
    return ". https://docs.Coral Health.io/types/ihc/v1/";
}
function storeMeta(Multihash record, IHCMetadata data) {
    ...
}
function getMeta(Multihash record) constant returns (IHCMetadata) {
    ...
}
```

Example initial standard data types:

- Genetic Test Results
 - BRCA1/BRCA2
 - MTHFR
- Lipid Markers Test Results
 - LDL, HDL, apolipoproteins, Lipoprotein (a)
- Inflammatory Markers Test Results
 - hs-CRP, TNFs, fibrinogen, interleukins
- Metabolic Biomarkers Test Results
 - Serum insulin levels
- Microbiology Test Results
 - Helicobacter pylori

6.4 Health Record Encryption

Medical record data files submitted to Coral Health will be symmetrically encrypted using aes-256-cbc. The arbitrary key generated by the client software is then encrypted with a patient's public key and stored by the Coral Health Ledger Smart Contract. By using an arbitrary key for symmetric encryption, Coral Health retains the flexibility to delegate records access to additional parties on a per-file basis, without resorting to storing additional re-encrypted copies. This allows for complex mechanisms governing record access to be developed while keeping the Coral Health Ledger simple, ensuring that patients and other stakeholders retain precise control over the accessibility of medical information.

To decrypt record data, a patient – through a client application – would consult the Coral Health Ledger Smart Contract to retrieve the record's encryption key, which itself is encrypted with the patient's public key. The patient would then use their public key to decrypt the encryption key, producing the key required to decrypt the actual record.

6.5 Health Record Storage

The blockchain possesses several key data properties that make it ideal for Coral Health's applications: it is immutable, decentralized, and highly accessible. However, the cost to store data on the blockchain is high, due to the time required to validate each block of data; if full medical data were to be stored on the blockchain, the system would be prohibitively slow. Coral Health therefore proposes to store the bulk of patient data off the blockchain, which would make it feasible to store and quickly access large volumes of data, and thus preserve the full richness of patient records. The secure-by-design properties of the blockchain would be preserved by encrypting the data, and storing the metadata, encryption keys, and hashes on the blockchain.

Coral Health has explored a number of data storage methods. The most promising storage method is to use the IPFS decentralized storage system as a blob store. The IPFS implementation offers a content-addressable storage namespace scheme in which the hash would be Base58 encoded and begin with the first two bytes 0x1220 (“Qm”) indicating that Coral Health uses a SHA256 hash truncated to 32 bytes. For example:

```
QmGK3MCWuij3KeVXWskLaBtoVtYjNvyGmcggy37YL9pgc.
```

The nature of this system allows for it to operate in tandem with other storage systems – such as Amazon’s S3 centralized data storage host – allowing for flexibility during initial adoption. During development, Coral Health would be conscious to avoid highly coupling to IPFS in order to maintain the flexibility to innovate unencumbered by dependencies on external systems.

Coral Health will populate the database initially using data provided by pilot partners. Existing datasets will be parsed using regular expressions, and automatically transferred to Coral Health’s predefined data structures, with any non-matches or parsing failures manually reviewed and inputted. Through the pilot, Coral Health will work with partners to propose a new database structure and user interface that would allow partners to easily interact with the IPFS database, and promote data standardization across players in the healthcare system.

With IPFS, Coral Health would initially operate a fleet of nodes that pin all data on the network; this would not only ensure data availability, but would also encourage participation by parties that may not be prepared to operate nodes independently. By nature, Coral Health would be motivated as the host of the data to ensure data availability and network health. Critically, IPFS also allows other parties to host redundant copies of the data, so that participants are not required to trust Coral Health to store their data indefinitely.

The IPFS database would be trivial to implement by observing the Coral Health Ledger Smart Contract on the Ethereum blockchain, recording the hash of every published medical record, and instructing the IPFS client to pin each hash. In doing this, Coral Health would be bootstrapping the network and ensuring that data would always be available. To retrieve files, the client would simply utilize an IPFS . HTTPS gateway.

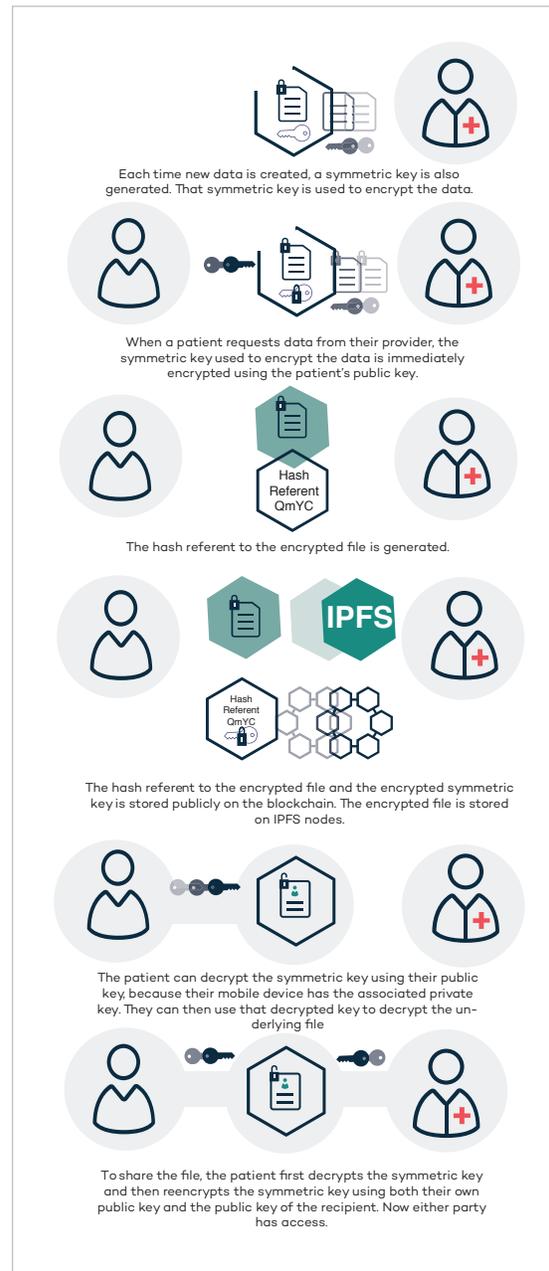
In addition to establishing its own network of nodes, Coral Health would encourage partner organizations to operate their own IPFS nodes that would mirror encrypted record files; these entities would be motivated to do so in order to ensure ease of accessibility. For example, a medical lab could operate nodes in order to ensure that the data they produce is more widely available on the network. There would be no restriction on who can mirror encrypted record files, so even technology enthusiasts may operate nodes to ensure that their own data is available to them. Since all the data that resides in the node is encrypted, data security would not be compromised.

6.6 Access Delegation

Patients will initially have the only decryption key to their data, and so are empowered to decide who may access it. Coral Health expects that patients will typically delegate access through smart contracts to some or all of their records to other parties, such as their healthcare provider, insurance company, hospital, or health authority.

To do so, a patient would consult the Coral Health Ledger Smart Contract to retrieve the record encryption key. The patient would then decrypt the key and re-encrypt it using the public key belonging to the intended recipient, submitting this information to the Coral Health Ledger Smart Contract in a transaction. The recipient would then be able to decrypt and read the records. Through the use of smart contracts, the recipient would also be able to delegate access to additional recipients, within parameters set by the patient.

This kind of transitive delegation allows for the formation of markets in which patients could allow access to their medical records in exchange for payment. For example, a pharmaceutical company could offer to pay patients for access to relevant data in their medical records. The patient could set their price – utilizing market-rate based suggestions provided by Coral Health – and delegate access to the pharmaceutical company through a series of smart contracts that would only delegate access after payment had been verified.



6.7 Client Applications

Coral Health will create client applications that allow partners and members of the general public to manage medical records, delegate access to data, execute transactions for data use, and more, without requiring participants to have any knowledge of the blockchain. Specialized client interfaces for mobile and web platforms will be developed sequentially, based on their expected utility in the context of Coral Health's overall growth.

Currently, Coral Health is developing an application allowing labs to print patients' test results to the blockchain. Patients are also able to view lab results through this interface, and grant permission for information to be stored on the blockchain. Coral Health plans on developing additional interfaces in the following order:

- **Interfaces for processing prescriptions.** This interface will allow doctors to share subscription information with insurance companies and pharmacies for easy coverage approval and fulfillment.
- **An interface to permit insurance companies to process and share medical policies via smart contracts.** This interface will allow for the automatic processing of claims and prior authorization requests.
- **A physician interface that will allow healthcare providers to review test results posted to the blockchain.** This interface will also allow doctors to communicate with patients, and will incorporate a marketplace through which physicians can provide health tips to interested patients.
- **A user interface for data decryption requests.** Health authorities and pharmaceutical companies will be able to view and search metadata to identify patients that meet research eligibility criteria; these organizations would then be able to send data decryption requests to selected patients, followed by payments to those patients who chose to participate.

The applications will have native support for popular data types – such as lab results and x-ray images – and data markets. Coral Health would also register a URI handler for Coral Health :// URIs in order to ensure that doctors and other stakeholders can initiate transactions from outside the applications and easily integrate client functionality into their own websites. In order to spur adoption, Coral Health would also provide application training to insurance companies, health authorities, and other entities adopting the applications.



7. SUPPORT FROM PUBLIC ENTITIES

Coral Health is well positioned to seek institutional support from a number of public health entities in both Canada and the United States; including funding agencies – such as Genome Canada, NSERC, CIHR, SSHR, and OCE – as well as government agencies, foundations, and advocacy groups. Coral Health has identified two funding agencies – Genome British Columbia and Genome Canada – that have promising potential for immediate engagement. Plans to secure funding from these agencies are detailed below. In addition to institutional funding, Coral Health will also seek “soft support” from other stake holders in the industry; efforts to this end are also described in this section.

7.1 Funding Through the I2 Program

Genome Canada functions on a two-tier system, funding large scale genomics research on a national level, and overseeing a network of provincial “Genome Centers” (collectively referred to as the “Genome Enterprise”), which support independent, comprehensive genomics initiatives regionally. Research initiatives eligible for funding include both focused genomics projects, which use high throughput technologies to study the genetic information of a cell or organism, as well as projects in related disciplines, such as bioinformatics, epigenomics, metabolomics, metagenomics, nutrigenomics, pharmacogenomics, proteomics, and transcriptomics. Within these areas, Genome Canada and the Genome Enterprise fund projects in all stages of development, from initial research to technology validation and commercialization. Genome Canada designs and launches funding programs, which are then administered primarily at the provincial level.

Genome Centers offer a support system that serves both academic and industry researchers seeking access to Genome Canada funding opportunities. Services also include connecting start-up companies in the industry with academic researchers, and providing strategic and scientific counsel to those seeking Genome Canada funding. In addition, many of the Genome Centers – including both Ontario Genomics and Genome British Columbia – provide direct investment capital for early stage companies through programs such as the Pre-Commercialization Business Development Fund (PBDF) and the Industry Innovation program (I2).

The I2 program provides direct support to companies that are in the early stages of developing and commercializing innovative life science technologies. Unlike many other efforts in the field, the I2 program is designed to support both direct genomics research and the development of technologies that enable the uptake of life science advances. The I2 program’s recent investments have included a number of digital health technologies that support personalized or precision medicine, making it an ideal funding vehicle for Coral Health.

The program would provide direct financial backing up to \$1,000,000 to support early commercialization efforts. Support would also include access to Genome British Columbia’s Advisory Council, which is comprised of veterans from pharmaceutical companies, technology manufacturers, diagnostic laboratories, and medical device manufacturers who are deeply connected to key stakeholder groups within British Columbia and across Canada. Through the Advisory Council, Coral Health would receive guidance on commercialization efforts, due diligence assistance, IP and marketing strategy support, and connections to key end user groups.

Direct support through the I2 program is feasible for Coral Health to obtain and would help lower barriers to subsequent investment capital. In order to pursue I2 program funding, Coral Health would need to submit a business plan – including a list of software-based deliverables, a projected budget, personnel requirements, a potential market analysis, and a timeline of achievable milestones – to Genome British Columbia, which would review the plan and advise on areas for development prior to formally submitting the plan for funding. Based on Coral Health’s current trajectory, the Company would plan on submitting a business plan to the I2 program within two to four months of a seed funding event.

7.2 Funding Through Genome Canada

Genome Canada operates strictly through competitive funding programs, such as the Large-Scale Applied Research Program, the Genomics Application Partnership Program, the Bioinformatics and Computational Biology Competition, the Genomics in Society Program, and the Disruptive Innovation in Genomics Program. By mandate, Genome Canada dollars from these programs flow exclusively to academic researchers, and cannot directly fund industry projects. However, Genome Canada’s funding programs typically require that academic researchers collaborate with an industry partner in order to obtain funding. Moreover, Genome Canada mandates that research funded by the program must have a clear path to uptake by end users, such as health care providers or other operators in the industry. As such, funding through Genome Canada offers a key development opportunity for Coral Health.

In order to obtain funding from Genome Canada, Coral Health would first establish partnership with academic researchers whose work complements Coral Health’s own research and development needs. Such a funded research proposal would allow the product of the academic research to flow directly to Coral Health. Coral Health’s own advisory team is well connected to Canadian researchers working in the genomics field, and would identify potential academic partners who could address the Company’s research needs. To fund exploratory meetings and initial partnered research, Coral Health would seek support from the NSERC Connect and Engage grants, which are designed to initiate industry-academic partnerships. These grants are not highly competitive and could likely be obtained within three to six months.

7.3 Soft Support

Coral Health will seek soft support from public entities in the form of letters and advocacy, in addition to the direct financial support described above. To this end, the Coral Health plans to engage with organizations that represent the interests of Coral Health’s end users, such as clinician groups, hospital associations, patient advocacy groups, insurance groups, and health authorities. Beginning discussions with these interest groups will help build a critical mass of support that would be leveraged to bring larger public and government entities onboard. Coral Health already has acquired memorandums of support from health data, health authority, and provider groups across North America.

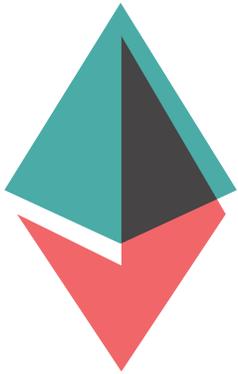
These support commitments range from resource allocation to future participation in pilot programs. The Canadian Organization for Rare Diseases – which advocates on behalf of over 120 patient groups and is closely connected to clinicians and government agencies – could offer another promising avenue of support. Once a relationship has been established with an interested group, Coral Health would seek to pilot with the selected organizations in order to provide proof-of-concept prior to a larger roll out.

A pilot program with a laboratory partner would initially involve selecting a single, popular test (for example, a urine or blood toxicology test). A web or mobile application will be provided to both the laboratory and participating patients through which information would be written to the Coral Health system and the lab's traditional data processing pipelines concurrently. Over several weeks, Coral Health and the laboratory would monitor patient satisfaction, data integrity, and data processing metrics collaboratively and then expand usage to additional tests. Coral Health anticipates that a pilot program would last for three to six months before a laboratory is ready to replace its existing systems with Coral Health.

Lab pilot programs will run in tandem with physician communities, based on available resources. Once sufficient data is amassed, the pilot program will be extended to payers, pharmacies, pharmaceutical and medical device companies, and health authorities.



8. CORAL HEALTH'S ROADMAP



Contingent on initial funds raised, Coral Health will prioritize the operational tasks outlined below. Business, administration, and software developments targets are outlined for the short-term, and may be executed concurrently; longer-term company objectives are also listed.

Note: The approximate timelines listed for short-term targets are subject to change; timelines for larger objectives will be determined throughout the execution and completion of short-term objectives.

8.1 Short-Term

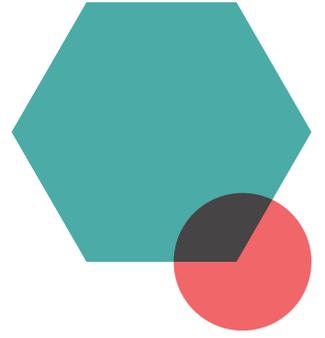
Milestone	Target Completion
Create beta versions of patient-lab user interface and patient-physician user interface to solicit pilot program participation	2Q18
Create full working version of patient-lab application to use in pilot	2Q18/3Q18
Hire additional sales, research & operations, and software development staff. Recruitment of senior level leadership in these areas has already begun. Coral Health currently already has accounting, legal, and support staff on contract.	2Q18/3Q18
Build alpha version of Coral Health patient-lab database, hosted on Amazon S3 interacting with the Ethereum main net (or potentially an isolated side chain)	3Q18
Create beta version of Coral Health-specific blockchain and integrate with IPFS (or similar distributed database)	3Q18
Create full working version of patient-physician interaction user interface within Coral Health application	3Q18
Solicit interest for additional pilot programs from laboratories and provider groups (including soft commitments already received)	4Q18
Begin conversion of seed pilot programs to full programs	4Q18

8.2 Mid-Term

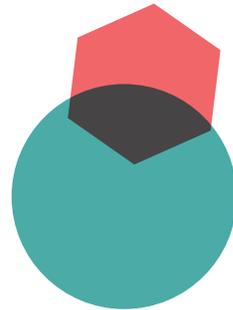
Milestone	Target Completion
Begin sales rollout of Coral Health system to diagnostic laboratories throughout the US and Canada	1Q19
Begin contracting process for pilot programs with payers in the US	1Q19
Build beta application for payers to read laboratory information posted through Coral Health	1Q19
Build initial smart contracts for a select set of medical policies for pilot payers, to be used in a standardized format with other payers	2Q19
Complete architecture for automated processing of smart contracts with laboratory data used as inputs	2Q19/3Q19
Provide user interface for payers to see recommended insurance adjudication based on lab results and internal medical policies	3Q19
Conduct pilot programs with seed payers	3Q19/4Q19
Approach provider groups and hospital chains for pilot programs	4Q19
Begin conversion of payer pilot programs to full programs	4Q19/1Q20
Begin sales rollout of Coral Health to payers throughout the US	1Q20

8.3 Long-Term

- Continue to scale smart contract and blockchain capabilities, potentially running on an Ethereum side chain and continue to evaluate optimal blockchain options
- Optimize data storage, continue optimizing operated node fleets (similar to the IPFS model)
- Integrate all major players in healthcare (patients, providers, payers, labs, pharmaceutical and medical device companies, pharmacies, and health authorities) into the Coral Health system
- Deeper patient participation initiatives through aggressive marketing
- Conduct pilot programs with medical device and pharmaceutical companies to identify qualified clinical trials candidates more quickly through the burgeoning Coral Health system
- Conduct pilot programs with public health authorities to monitor new and latent symptoms appearing in the Coral Health blockchain, aid in public health messaging initiatives
- Approach university laboratories and research clusters for partnership opportunities related to personalized medicine
- Geographic expansion of pilot programs (advisory group has hospital executive contacts in multiple South American countries)



9. BIBLIOGRAPHY

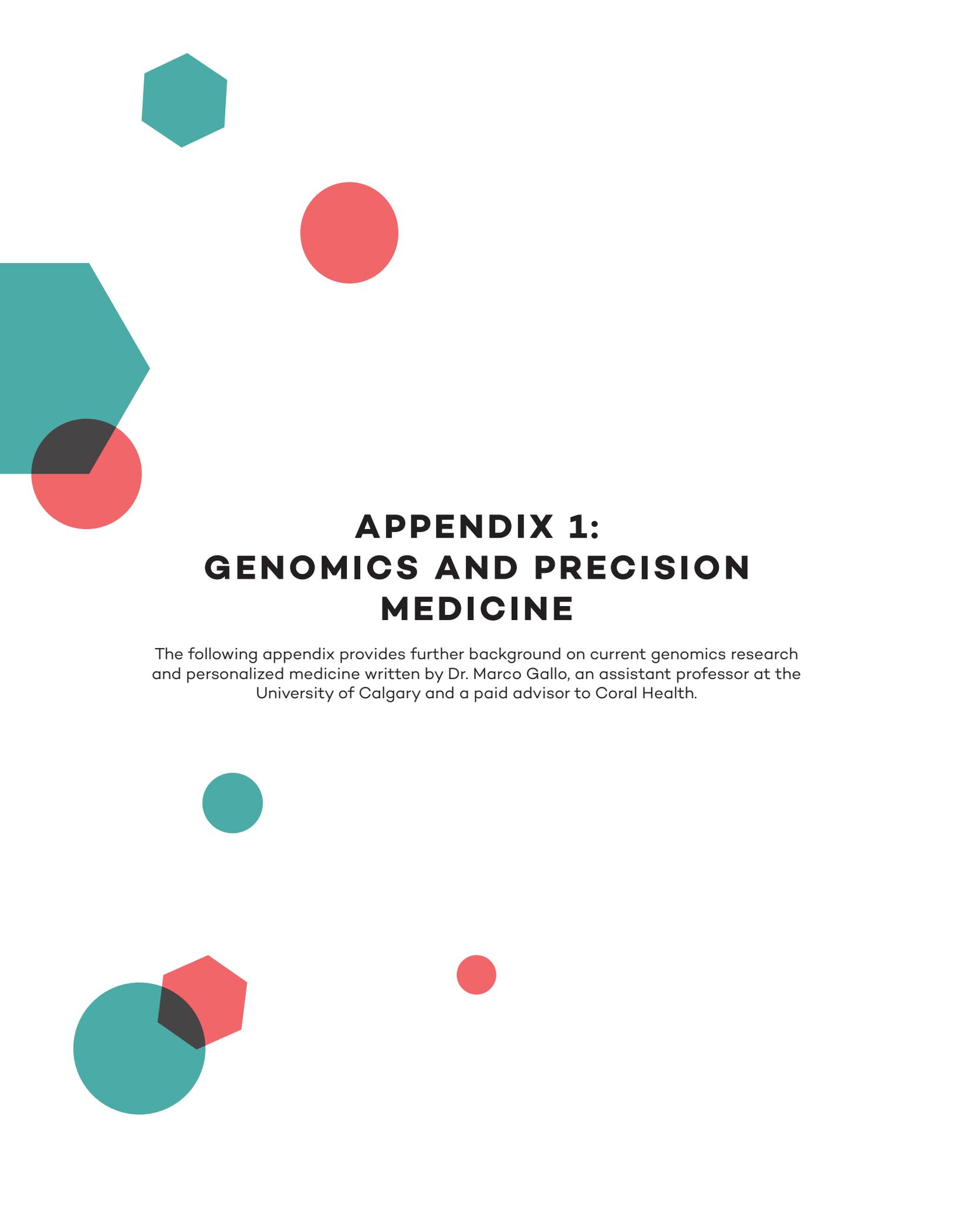


1. FDA. Paving the Way for Personalized Medicine: FDA's Role in a New Era of Medical Product Development FDA's Role in a New Era of Medical Product Development. <https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PersonalizedMedicine/UCM372421.pdf> (accessed 18 November 2017).
2. Olson S. Integrating large-scale genomic information into clinical practice: workshop summary. *Natl Acad Press* 2012; 92.
3. An Overview of the Human Genome Project. National Human Genome Research Institute. <https://www.genome.gov/12011238/an-overview-of-the-human-genome-project/> (accessed 2 December 2017).
4. Health IT Legislation and Regulation. HealthIT.gov. <https://www.healthit.gov/policy-researchers-implementers/health-it-legislation> (accessed 2 December 2017).
5. Office-based Physician Electronic Health Record Adoption. The Office of the National Coordinator for Health Information Technology. <https://dashboard.healthit.gov/quickstats/pages/physician-ehr-adoption-trends.php> (accessed 2 December 2017).
6. Adoption of Electronic Health Record Systems among U.S. Non-Federal Acute Care Hospitals: 2008-2015. The Office of the National Coordinator for Health Information Technology. <https://dashboard.healthit.gov/evaluations/data-briefs/non-federal-acute-care-hospital-ehr-adoption-2008-2015.php> (accessed 2 December 2017).
7. Hampel H, O'Bryant SE, Castrillo JI, et al. PRECISION MEDICINE - The Golden Gate for Detection, Treatment and Prevention of Alzheimer's Disease. *J Prev Alzheimer's Dis* 2016; 3: 243-259.
8. Vogenberg FR, Barash CI, Pursel M. Personalized medicine: part 2: ethical, legal, and regulatory issues. *P T* 2010; 35: 624-42.
9. Genentech: Press Releases. <https://www.gene.com/media/press-releases/7947/2004-11-18/fda-approves-tarceva-for-patients-with-a> (accessed 2 December 2017).
10. Cohen MH, Williams GA, Sridhara R, et al. FDA drug approval summary: gefitinib (ZD1839) (Iressa) tablets. *Oncologist* 2003; 8: 303-6.
11. FDA Gives Fast Approval to Gleevec in Treatment of CML | Cancer Network | The Oncology Journal. ModernMedicine Network, 1 June 2001. <http://www.cancernetwork.com/chronic-myeloid-leukemia/fda-gives-fast-approval-gleevec-treatment-cml> (1 June 2001, accessed 2 December 2017).
12. Cohen P. Protein kinases — the major drug targets of the twenty-first century? *Nat Rev Drug Discov* 2002; 1: 309-315.
13. Wu P, Nielsen TE, Clausen MH. Small-molecule kinase inhibitors: an analysis of FDA-approved drugs. *Drug Discov Today* 2016; 21: 5-10.
14. Zhang J, Salminen A, Yang X, et al. Effects of 31 FDA approved small-molecule kinase inhibitors on isolated rat liver mitochondria. *Arch Toxicol* 2017; 91: 2921-2938.

15. Schilsky RL. Personalized medicine in oncology: The future is now. *Nat Rev Drug Discov* 2010; 9: 363–366.
16. Kwak EL, Bang Y-J, Camidge DR, et al. Anaplastic Lymphoma Kinase Inhibition in Non-Small-Cell Lung Cancer. *N Engl J Med* 2010; 363: 1693–1703.
17. The 100,000 Genomes Project. Genomics England. <https://www.genomicsengland.co.uk/the-100000-genomes-project/> (accessed 2 December 2017).
18. Newbern E. Canada's iTARGET Consortium Aims to Develop Multi-Omics-Based Diagnostic Tools for Autism. *genome web*, 19 April 2017. <https://www.genomeweb.com/sequencing/canadas-itar-get-consortium-aims-develop-multi-omics-based-diagnostic-tools-autism> (19 April 2017, accessed 2 December 2017).
19. Connected Care and the Patient Experience. Surescripts. <http://surescripts.com/connectedpatient/default.html#emotions> (accessed 3 December 2017).
20. Kliff S. The fax of life. *Vox*, 30 October 2017. <https://www.vox.com/health-care/2017/10/30/16228054/american-medical-system-fax-machines-why> (30 October 2017, accessed 23 November 2017).
21. O'Malley AS, Grossman JM, Cohen GR, et al. Are Electronic Medical Records Helpful for Care Coordination? Experiences of Physician Practices. *J Gen Intern Med* 2010; 25: 177–185.
22. Bodenheimer T. Coordinating Care — A Perilous Journey through the Health Care System. *N Engl J Med* 2008; 358: 1064–1071.
23. Bush J, Fox J. Bringing the Power of Platforms to Health Care. *HBR*. <https://hbr.org/2016/11/bringing-the-power-of-platforms-to-health-care> (accessed 3 December 2017).
24. Schoen C, Osborn R, Huynh PT, et al. Primary Care And Health System Performance: Adults' Experiences In Five Countries. *Health Aff* 2004; Suppl Web Exclusives: W4-487–503.
25. Forrest CB, Glade GB, Baker AE, et al. Coordination of specialty referrals and physician satisfaction with referral care. *Arch Pediatr Adolesc Med* 2000; 154: 499–506.
26. Gandhi TK. Fumbled handoffs: one dropped ball after another. *Ann Intern Med* 2005; 142: 352–8.
27. Kripalani S, LeFevre F, Phillips CO, et al. Deficits in Communication and Information Transfer Between Hospital-Based and Primary Care Physicians. *JAMA* 2007; 297: 831.
28. Hackbarth AD, Hackbarth AD. Eliminating Waste in US Health Care. *JAMA* 2012; 307: 1513.
29. Lawrence P, Casalino, Sean Nicholson, David N. Gans, Terry Hammons, Dante Morra, Theodore Karrison WL. What Does It Cost Physician Practices To Interact With Health Insurance Plans?
30. Sahni N, Anuraag C, Kocher B, et al. How the U.S. Can Reduce Waste in Health Care Spending by \$1 Trillion. *HBR*. <https://scholar.harvard.edu/cutler/news/how-us-can-reduce-waste-health-care-spending-1-trillion> (2015, accessed 2 December 2017).

31. DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: New estimates of R&D costs. *J Health Econ* 2016; 47: 20–33.
32. Reed MD. The Rescue and Repurposing of Pharmaceuticals: Augmenting the Drug Development Paradigm. *J Pediatr Pharmacol Ther* 2016; 21: 4–6.
33. Oprea TI, Mestres J. Drug Repurposing: Far Beyond New Targets for Old Drugs. *AAPS J* 2012; 14: 759–763.
34. Carlisle B, Kimmelman J, Ramsay T, et al. Unsuccessful trial accrual and human subjects protections: An empirical analysis of recently closed trials. *Clin Trials* 2015; 12: 77–83.
35. Biopharmaceutical Industry-Sponsored Clinical Trials: Impact on State Economies. Battelle Technology Partnership Practice. <http://phrma-docs.phrma.org/sites/default/files/pdf/biopharmaceutical-industry-sponsored-clinical-trials-impact-on-state-economies.pdf>? (2015, accessed 2 December 2017).
36. Schulthess D, Duane G. Opt-in, Opt-out, & Patient Led Databases. https://vitaltransformation.com/wp-content/uploads/2014/10/DGS_17-10-Opt-in-Opt-out-Patient-Led-Databases-MAPPs-DG3.pdf (accessed 2 December 2017).
37. Xu H, Aldrich MC, Chen Q, et al. Validating drug repurposing signals using electronic health records: a case study of metformin associated with reduced cancer mortality. *J Am Med Informatics Assoc* 2014; 22: 179–191.
38. Yao L, Zhang Y, Li Y, et al. Electronic health records: Implications for drug discovery. *Drug Discov Today* 2011; 16: 594–599.
39. Paik H, Chung A-Y, Park H-C, et al. Repurpose terbutaline sulfate for amyotrophic lateral sclerosis using electronic medical records. *Sci Rep* 2015; 5: 8580.
40. Khatri P, Roedder S, Kimura N, et al. A common rejection module (CRM) for acute rejection across multiple organs identifies novel therapeutics for organ transplantation. *J Exp Med* 2013; 210: 2205–2221.
41. Retrospective Study Suggests that Patients with Lung Cancer who Carry Specific HER2 Mutations May Benefit from Certain Anti-HER2 Treatments. American Society of Clinical Oncology (ASCO). <http://www.newswise.com/articles/retrospective-study-suggests-that-patients-with-lung-cancer-who-carry-specific-her2-mutations-may-benefit-from-certain-anti-her2-treatments> (accessed 3 December 2017).
42. Ray S. Assessing the Value of Retrospective Studies Real World Data Real World Applications. *Pharmaceutical Executive*, 1 August 2013. <http://www.pharmexec.com/assessing-value-retrospective-studies-real-world-data-real-world-applications> (1 August 2013, accessed 3 December 2017).
43. Summary of the HIPAA Privacy Rule. HHS.gov. <https://www.hhs.gov/hipaa/for-professionals/privacy/laws-regulations/index.html> (accessed 2 December 2017).
44. EU General Data Protection Regulation (GDPR). <https://gdpr-info.eu/> (accessed 2 December 2017).
45. Lord N. Top 10 Biggest Healthcare Data Breaches of All Time | Digital Guardian. *Digital Guardian*, 28 March 2017. <https://digitalguardian.com/blog/top-10-biggest-healthcare-data-breaches-all-time> (28 March 2017, accessed 23 November 2017).

46. Herman B. Details of Anthem's massive cyberattack remain in the dark a year later - Modern Healthcare. Modern Healthcare, 30 March 2016. <http://www.modernhealthcare.com/article/20160330/NEWS/160339997> (30 March 2016, accessed 23 November 2017).
47. Nakamoto S. Bitcoin: A Peer-to-Peer Electronic Cash System www.bitcoin.org (accessed 2 December 2017).
48. What is pharmacogenomics? U.S. National Library of Medicine. <https://ghr.nlm.nih.gov/primer/genomicresearch/pharmacogenomics> (accessed 2 December 2017).
49. Woods SS, Schwartz E, Tuepker A, et al. Patient experiences with full electronic access to health records and clinical notes through the My HealthVet Personal Health Record Pilot: qualitative study. *J Med Internet Res* 2013; 15: e65.
50. Linder JA, Schnipper JL, Tsurikova R, et al. Barriers to electronic health record use during patient visits. *AMIA . Annu Symp proceedings AMIA Symp* 2006; 499–503.
51. Roden D, Pulley J, Basford M, et al. Development of a Large-Scale De-Identified DNA Biobank to Enable Personalized Medicine. *Clin Pharmacol Ther* 2008; 84: 362–369.
52. Jeffrey Bendix SE. Curing the prior authorization headache. *Med Econ*. <http://medicaleconomics.modernmedicine.com/medical-economics/content/tags/americas-health-insurance-plans/curing-prior-authorization-headache> (2013, accessed 3 December 2017).
53. Jiwani A, Himmelstein D, Woolhandler S, et al. Billing and insurance-related administrative costs in United States' health care: synthesis of micro-costing evidence. *BMC Health Serv Res*; 14. Epub ahead of print 2014. DOI: 10.1186/s12913-014-0556-7.
54. FDA. Questions and Answers on FDA's Adverse Event Reporting System (FAERS). <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/> (accessed 2 December 2017).
55. FDA. Guidance for Clinical Investigators, Sponsors, and IRBs. <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm> (accessed 2 December 2017).
56. CDC. Overview of Influenza Surveillance in the United States. <https://www.cdc.gov/flu/weekly/overview.htm> (accessed 2 December 2017).
57. Thompson WW, Comanor L, Shay DK. Epidemiology of Seasonal Influenza: Use of Surveillance Data and Statistical Models to Estimate the Burden of Disease. *J Infect Dis* 2006; 194: S82–S91.



APPENDIX 1: GENOMICS AND PRECISION MEDICINE

The following appendix provides further background on current genomics research and personalized medicine written by Dr. Marco Gallo, an assistant professor at the University of Calgary and a paid advisor to Coral Health.

Overview

Traditionally, fundamental and biomedical science have investigated the causal and functional links between a single molecule and a specific phenotype or disease. Disruptive technological advances over the last twenty years have permitted the concurrent analysis of networks of thousands of molecules that define specific disease states. The ability to comprehensively investigate complex molecular changes associated with disease is a defining feature of the

“-omics” revolution, and has represented a significant paradigm shift in the way we study and think of disease. Below, we provide a description of the main -omics players in the context of precision medicine.

Genomics

The study of the links between mutations in a single gene and a given phenotype has traditionally been the realm of genetics. In recent years, we have been able to look at all the genetic changes occurring in the genome in one single test or experiment, ushering in the field of genomics. This transformational change has its roots in two foundational events: (1) The sequencing and assembly of the first human reference genome^{1,2}; (2) The advent of next-generation sequencing (reviewed in reference 3). The latter has allowed high throughput sequencing through the generation of short reads, which can then be aligned to the reference genome through computational algorithms. The combination of these two factors has led to the ability to perform whole-genome sequencing for approximately \$1,000 as of this year.

Another important genomic application that is becoming prevalent in research studies is transcriptomic profiling by RNA sequencing (RNA-seq)⁴. RNA is a molecule produced when a gene is turned on (Figure 1). Massively parallel sequencing technology has allowed genome-wide profiling of gene expression, which represents a measure of how active a gene is. RNA-seq experiments have highlighted significant difference between disease and healthy tissues.

Parallel developments in other fields have also led to the ability to examine multiple (sometime thousands) of molecules in a single experiment (Figure 1). One example is provided by PROTEOMICS, which consists of the study of protein repertoires associated with a specific phenotype (reviewed in reference 5). Proteins are encoded by our genome (Figure 1), and are the executioner of most functions that are necessary for a cell to function. Similarly, METABOLOMICS studies metabolites that are associated with specific phenotypes (reviewed in reference 6). Metabolites are small molecules that are usually produced through chemical reactions mediated by proteins. Genome Canada considers proteomics and metabolomics to fall within the definition of genomics⁷ because of the intimate link between genes, proteins, and metabolites (Figure 1). Proteomics and metabolomics hold tremendous potential for the discovery of biomarkers with diagnostic or prognostic value. However, the wide dynamic range for proteins and their post-translational modifications, and for metabolites, prohibits the identification of the full repertoire of molecules present in samples for proteomics and metabolomic studies with current technology. On the contrary, the finite nature of the mapped reference genome allows for hard determinations of all genomic changes occurring in a given sample.

Epigenomics

This discipline studies heritable chemical modifications of DNA that are independent of mutations, and chemical modifications of histones, which are proteins used to tightly pack the two-metre human genome into the confined space of a single nucleus. Different DNA and histone modifications result either in tighter or looser packaging of the DNA at any specific site along the genome. Epigenomics has exploited the same technical advances that have spurred genomics to map DNA and histone chemical modifications genome-wide, in normal tissues and disease states, including cancer. The degree of DNA compaction acts as a rheostat to determine the degree of activation of a gene. In general, tightly packed DNA results in repression of gene expression, whereas looser DNA architecture leads to activation of a gene⁸. Therefore, epigenomic events have a fundamental role in determining the levels of gene expression in healthy and diseased tissues.

Genomics and Epigenomics in Disease

Both genomic and epigenomic aberrations have been identified in disease, especially in cancer. The most common genomic aberrations consist of changes to the building blocks of DNA – called mutations – or losses of DNA fragments (deletions), gains of DNA, and translocations of DNA between different chromosomes, among others. All of the disease-causing DNA aberrations in genes affect the ability of the encoded protein to properly function, or cause the production of insufficient or too much protein. In cancer, it is common to observe activating mutations in oncogenes, or deletions and deleterious mutations in tumor suppressor genes⁹.

Epigenomic aberrations contribute to disease by shaping gene expression profiles. Recent studies have shown that tumors tend to have lower levels of a chemical modification called methyl group on DNA, compared to matched normal tissue^{10,11}. DNA methylation is a classical epigenetic mark and if found upstream of a gene, it usually leads to DNA compaction and repression of gene expression¹². The hypomethylated genomes of tumors cause aberrant gene expression profiles that promote tumorigenesis and/or tumor growth.

There are also examples of mutations in the DNA that affect the epigenome and the expression of downstream genes, highlighting an important functional crosstalk between the genome and the epigenome. It was noted that most DNA single nucleotide variants in cancer samples reside outside of genes¹³⁻¹⁵, in regions that were until recently thought of as “junk DNA.” In reality, these regions are rich in epigenetic elements that determine the levels of expression of genes¹⁶, thereby acting as switches for the activation or repression of genes. Mutations in these “switch” regions affect their abilities to properly regulate gene expression and may lead to disease, including cancer (Figure 2). This latest example shows how tightly genomic and epigenomic factors can cooperate in the evolution of disease.

Genomics in Precision Medicine

Information about individuals' genomes has had a significant impact on the treatment of several cancer types. A classic example of this is the identification of a chromosomal translocation that occurs in 95% of chronic myelogenous leukemia (CML) patients¹⁷.

This translocation causes the fusions of two genes – BCR and ABL – that are normally on two separate chromosomes, and results in the production of a BCR-ABL protein that acts as a constitutively active tyrosine kinase^{18,19}. The discovery of this genetic anomaly that is specific to malignant cells resulted in the development of Imatinib (Gleevec®)²⁰, an inhibitor of the BCR-ABL oncoprotein. Imatinib was incredibly effective at prolonging survival of CML patients²¹, with a significant cohort achieving long-term complete cytogenetic responses²², and was approved by the FDA for treatment of individuals with BCR-ABL translocations in 2001.

More recent genomic efforts have identified new molecular targets that could potentially benefit therapeutic approaches for multiple cancer types. One example is the identification of EZH2 as a promising oncology target²³. Transcriptomic (RNA-seq) data have shown that EZH2 is expressed at high levels in many cancer types, including breast cancer²⁴, melanoma²⁵ and glioblastoma^{26,27}. Furthermore, genome sequencing has identified a significant cohort of Non-Hodgkin's lymphomas carrying activating mutations in EZH2²⁸⁻³¹, i.e. mutations that potentiate the function of this enzyme. As a consequence, EPZ-6438 (Tazemetostat), a compound that inhibits EZH2, is in phase I/II clinical trials for patients with B-cell lymphomas and advanced solid tumors (ClinicalTrials.gov ID NCT01897571). This is an example of rational drug deployment based on integration of transcriptomic and genomic datasets in specific tumor types, and a promising beginning for precision medicine approaches.

The Promise of Genomics and Epigenomics in Precision Medicine

The evolving technologies for next-generation sequencing are pushing down the costs for genomic assays. It is my opinion that soon the cost curves for genomic assays and standard clinical laboratory tests will converge. This means that it will be soon more economical to perform whole-genome sequencing for a patient than to sequence cancer gene panels, or perform cytology exams to identify individual chromosomal aberrations. Whole-genome sequencing will identify germline variants known to be associated with predisposition to certain diseases and familial cancers. Although most malignancies are caused by somatic mutations, banked whole-genome sequences will allow ready identification of tumor-specific mutations, thereby streamlining the process of identification of driver mutations, with implications for the choice of actionable targets and the design of therapeutic regimes.

Epigenomic analysis of cancer tissue may also become a standard tool to design personalized treatments. This is because academic and pharmaceutical endeavors have been generating compounds that target enzymes involved in regulation of the epigenome by depositing or erasing DNA or histone modifications. Given the progressively larger armamentarium of epigenetic drugs – or epidrugs – it is becoming increasingly more conceivable that if a specific epigenetic aberration is observed in a disease state, it may be corrected with an appropriate epidrug. Epigenetic marks are reversible, unlike DNA mutations, and therefore this approach is theoretically feasible. Correcting the epigenome might be an important therapeutic approach for pediatric cancers, which tend to have a paucity of DNA mutations, but are often characterized by significantly abnormal epigenomes³². As a proof of concept, a recent study showed that posterior fossa ependymoma – a type of aggressive brain tumor affecting infants and young children – have high levels of DNA methylation at very specific sites of the genome³³.

Using cells from a patient's biopsy, the researchers showed that a DNA demethylating agent was effective at curbing the growth of these cells in vitro. These preclinical data were sufficiently strong to grant a phase I/IIb clinical trial to test the effects of the DNA demethylating agent 5'-Azacitidine on pediatric brain tumor patients (ClinicalTrials.gov ID NCT03206021). This type of precision medicine initiative is particularly important for pediatric cancers, because these tumors tend to be molecularly different from their adult counterparts, but their relative rarity poses significant challenges in generating appropriate preclinical models to identify suitable therapeutics.

Bibliography

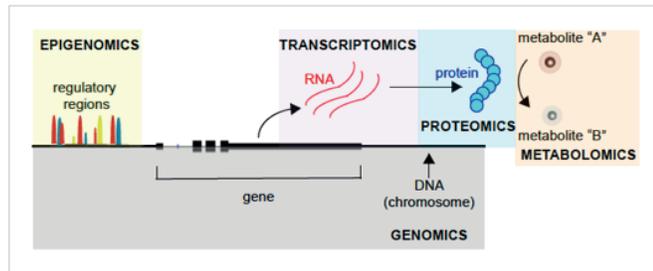
1. Lander ES, Linton LM, Birren B, Nusbaum C, Zody MC, Baldwin J, et al. Initial sequencing and analysis of the human genome. *Nature*. 2001;409(6822):860-921.
2. Venter JC, Adams MD, Myers EW, Li PW, Mural RJ, Sutton GG, et al. The sequence of the human genome. *Science*. 2001;291(5507):1304-51.
3. Metzker ML. Sequencing technologies - the next generation. *Nat Rev Genet*. 2010;11(1):31-46.
4. Mortazavi A, Williams BA, McCue K, Schaeffer L, Wold B. Mapping and quantifying mammalian transcriptomes by RNA-Seq. *Nat Methods*. 2008;5(7):621-8.
5. Graves PR, Haystead TA. Molecular biologist's guide to proteomics. *Microbiol Mol Biol Rev*. 2002;66(1):39-63; table of contents.
6. Roessner U, Bowne J. What is metabolomics all about? *Biotechniques*. 2009;46(5):363-5.
7. Genome Canada [Available from: <https://www.genomecanada.ca/en/why-genomics/understanding-code-life>].
8. Buenrostro JD, Giresi PG, Zaba LC, Chang HY, Greenleaf WJ. Transposition of native chromatin for fast and sensitive epigenomic profiling of open chromatin, DNA-binding proteins and nucleosome position. *Nat Methods*. 2013;10(12):1213-8.
9. Brennan CW, Verhaak RG, McKenna A, Campos B, Noushmehr H, Salama SR, et al. The somatic genomic landscape of glioblastoma. *Cell*. 2013;155(2):462-77.
10. Eden A, Gaudet F, Waghmare A, Jaenisch R. Chromosomal instability and tumors promoted by DNA hypomethylation. *Science*. 2003;300(5618):455.
11. Feinberg AP, Vogelstein B. Hypomethylation distinguishes genes of some human cancers from their normal counterparts. *Nature*. 1983;301(5895):89-92.
12. Schubeler D. Function and information content of DNA methylation. *Nature*. 2015;517(7534):321-6.
13. Khurana E, Fu Y, Chakravarty D, Demichelis F, Rubin MA, Gerstein M. Role of non-coding sequence variants in cancer. *Nat Rev Genet*. 2016;17(2):93-108.
14. Bailey SD, Desai K, Kron KJ, Mazrooei P, Sinnott-Armstrong NA, Treloar AE, et al. Noncoding somatic and inherited single-nucleotide variants converge to promote ESR1 expression in breast cancer. *Nat Genet*. 2016;48(10):1260-6.
15. Akhtar-Zaidi B, Cowper-Sal-lari R, Corradin O, Saiakhova A, Bartels CF, Balasubramanian D, et al. Epigenomic enhancer profiling defines a signature of colon cancer. *Science*. 2012;336(6082):736-9.
16. Katainen R, Dave K, Pitkanen E, Palin K, Kivioja T, Valimaki N, et al. CTCF/cohesin-binding sites are frequently mutated in cancer. *Nat Genet*. 2015;47(7):818-21.

17. Faderl S, Talpaz M, Estrov Z, Kantarjian HM. Chronic myelogenous leukemia: biology and therapy. *Ann Intern Med.* 1999;131(3):207-19.
18. Daley GQ, Van Etten RA, Baltimore D. Induction of chronic myelogenous leukemia in mice by the P210bcr/abl gene of the Philadelphia chromosome. *Science.* 1990;247(4944):824-30.
19. Kelliher MA, McLaughlin J, Witte ON, Rosenberg N. Induction of a chronic myelogenous leukemia-like syndrome in mice with v-abl and BCR/ABL. *Proc Natl Acad Sci U S A.* 1990;87(17):6649-53.
20. Druker BJ, Tamura S, Buchdunger E, Ohno S, Segal GM, Fanning S, et al. Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells. *Nat Med.* 1996;2(5):561-6.
21. Druker BJ, Guilhot F, O'Brien SG, Gathmann I, Kantarjian H, Gattermann N, et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. *N Engl J Med.* 2006;355(23):2408-17.
22. Palandri F, Iacobucci I, Martinelli G, Amabile M, Poerio A, Testoni N, et al. Long-term outcome of complete cytogenetic responders after imatinib 400 mg in late chronic phase, philadelphia-positive chronic myeloid leukemia: the GIMEMA Working Party on CML. *J Clin Oncol.* 2008;26(1):106-11.
23. Kim KH, Roberts CW. Targeting EZH2 in cancer. *Nat Med.* 2016;22(2):128-34
24. Varambally S, Dhanasekaran SM, Zhou M, Barrette TR, Kumar-Sinha C, Sanda MG, et al. The polycomb group protein EZH2 is involved in progression of prostate cancer. *Nature.* 2002;419(6907):624-9.
25. Bachmann IM, Halvorsen OJ, Collett K, Stefansson IM, Straume O, Haukaas SA, et al. EZH2 expression is associated with high proliferation rate and aggressive tumor subgroups in cutaneous melanoma and cancers of the endometrium, prostate, and breast. *J Clin Oncol.* 2006;24(2):268-73.
26. Lee J, Son MJ, Woolard K, Donin NM, Li A, Cheng CH, et al. Epigenetic-mediated dysfunction of the bone morphogenetic protein pathway inhibits differentiation of glioblastoma-initiating cells. *Cancer Cell.* 2008;13(1):69-80.
27. Kim E, Kim M, Woo DH, Shin Y, Shin J, Chang N, et al. Phosphorylation of EZH2 activates STAT3 signaling via STAT3 methylation and promotes tumorigenicity of glioblastoma stem-like cells. *Cancer Cell.* 2013;23(6):839-52.
28. Yap DB, Chu J, Berg T, Schapira M, Cheng SW, Moradian A, et al. Somatic mutations at EZH2 Y641 act dominantly through a mechanism of selectively altered PRC2 catalytic activity, to increase H3K27 trimethylation. *Blood.* 2011;117(8):2451-9.
29. Morin RD, Johnson NA, Severson TM, Mungall AJ, An J, Goya R, et al. Somatic mutations altering EZH2 (Tyr641) in follicular and diffuse large B-cell lymphomas of germinal-center origin. *Nat Genet.* 2010;42(2):181-5.
30. Sneeringer CJ, Scott MP, Kuntz KW, Knutson SK, Pollock RM, Richon VM, et al. Coordinated activities of wild-type plus mutant EZH2 drive tumor-associated hypertrimethylation of lysine 27 on histone H3 (H3K27) in human B-cell lymphomas. *Proc Natl Acad Sci U S A.* 2010;107(49):20980-5.
31. McCabe MT, Graves AP, Ganji G, Diaz E, Halsey WS, Jiang Y, et al. Mutation of A677 in histone methyltransferase EZH2 in human B-cell lymphoma promotes hypertrimethylation of histone H3 on lysine 27 (H3K27). *Proc Natl Acad Sci U S A.* 2012;109(8):2989-94.

32. Fontebasso AM, Gayden T, Nikbakht H, Neirinck M, Papillon-Cavanagh S, Majewski J, et al. Epigenetic dysregulation: a novel pathway of oncogenesis in pediatric brain tumors. *Acta Neuropathol.* 2014;128(5):615-27.
33. Mack SC, Witt H, Piro RM, Gu L, Zuyderduyn S, Stutz AM, et al. Epigenomic alterations define lethal CIMP-positive ependymomas of infancy. *Nature.* 2014.

Figures

Figure 1. Areas of interest for different –omics disciplines. The genome is interspersed with genes, which are usually used as templates to produce RNA. RNA is then translated by the cell machinery into proteins. Some proteins have enzymatic functions, and can process the conversion of a metabolite into another via specific chemical reactions. However, not all genes are protein coding. Strictly speaking, genomics studies changes in the DNA sequence genome-wide. Proteomics assesses the proteins that constitute the proteome of a cell type. Metabolomics investigates the metabolites present in a cell or tissue type. Since epigenomic elements control gene expression, the separation between epigenomics and transcriptomics is not absolute.



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Figure 2. Crosstalk between genomic and epigenomic events. Enhancer elements are regions that can control expression of genes. Enhancers are characterized by characteristic chemical modifications of histones (in green in the diagram). Functional enhancers interact with proteins that cause bending of the DNA, and recruit proteins that can activate gene expression (transcriptional complex) to a target gene. In cancer and other diseases, DNA mutations may cause loss of activity of enhancer elements, with consequent change in activity of downstream genes.

