Title
Precision medicine in chronic disease management: The multiple sclerosis BioScreen

Permalink
https://escholarship.org/uc/item/97n4p31g

Journal
Annals of Neurology, 76(5)

ISSN
0364-5134

Authors
Gourraud, PA
Henry, RG
Cree, BAC
et al.

Publication Date
2014-01-01

DOI
10.1002/ana.24282

Peer reviewed
We present a precision medicine application developed for multiple sclerosis (MS): the MS BioScreen. This new tool addresses the challenges of dynamic management of a complex chronic disease; the interaction of clinicians and patients with such a tool illustrates the extent to which translational digital medicine—that is, the application of information technology to medicine—has the potential to radically transform medical practice. We introduce 3 key evolutionary phases in displaying data to health care providers, patients, and researchers: visualization (accessing data), contextualization (understanding the data), and actionable interpretation (real-time use of the data to assist decision making). Together, these form the stepping stones that are expected to accelerate standardization of data across platforms, promote evidence-based medicine, support shared decision making, and ultimately lead to improved outcomes.

A Yet-to-Come Information Technology Revolution in Biomedicine

Information technology (IT) has enabled profound transformations in many industries, providing easier access to information of heterogeneous formats in a quasi-instantaneous and ubiquitous manner.¹ These transformations require the adaptation of long-established practices and demand new models, in terms of both practical outcomes and user expectations. Biomedicine is a notable exception. Almost 20 years after the seminal article published by Powsner and Tufte introducing graphical display of an individual patient’s status,² and despite considerable advances in biology, imaging technology, and therapeutics,³⁴ the field has yet to fully benefit from the IT revolution to integrate clinical and biomarker data of various types for research, or to deploy “big (biomedical) data” in a modern practice environment.⁵⁶ The reasons for this delay are many and include the independent nature of medical subdisciplines; the focus of electronic medical record priorities on compliance and billing rather than clinical research; a paucity of prospectively ascertained, deeply interrogated patient cohorts to support decision analysis; and a failure to standardize recording of clinical outcomes, neuroimaging platforms,
or even laboratory values. As digital health and IT are redefining access to health measures and research data, the traditional practice of disease-based taxonomy itself is being called into question. Unprecedented opportunities are created to tailor the practice of medicine to individual patients rather than to rely solely on evidence from heterogeneous populations who carry a common diagnosis.\(^2,8\)

The democratization of medical data, exemplified by direct-to-consumer testing and patients assuming increasing responsibility for maintaining their personal medical records, represents another sea change fueled by electronic technology. The profusion of data now available to and about each of us as individuals enables both patient empowerment and new insights for patients, caregivers, and researchers on the disease. The application of sophisticated IT tools and powerful data analytics to health is creating conditions for improved, and also innovative, models of care. Such sophisticated systems already enable businesses to recommend relevant products based on a customer’s purchase history. It is likely that similar yet more elaborate models will be applicable to development of useful software, computed from large arrays of biomedical patient data, to adapt disease assessment and treatment recommendations. The primary difference between health care and other industries lies in the availability and utility of data sets at hand; traditional consumer-based programs require relatively simple data types that are often readily available at large scale. In contrast, clinical record, imaging, and biomarker information comprises multiple data types that are often sparse, nonstandardized, collected over several years, and protected behind privacy firewalls.

Chronic medical conditions now consume 10% of the gross domestic product in the United States, 73% of all health care costs ($2 trillion USD), and >50% of all drug costs.\(^9,10\) These disorders are also characterized by their complexity; they are etiologically heterogeneous, resulting from the interplay of genes and environment, and expression is typically diverse, ranging from extremely mild to very aggressive courses. Chronic diseases also exhibit the property of emergence, meaning that their underlying biology is likely to be understood only by the integration of multiple factors. It is not yet possible for even the most expert clinicians to predict how most diseases will evolve in an individual patient or to anticipate a treatment’s safety or efficacy in that patient.

A Precision Medicine Tool for Multiple Sclerosis

Multiple sclerosis (MS) is a model condition to highlight the challenges and opportunities inherent to data integration for a complex disease. MS is the leading cause of nontraumatic neurological disability in the developed world, affecting 3 million people.\(^11,12\) The prevalence of MS has also dramatically increased in recent years.\(^13\) High-cost therapeutics for MS (the market currently exceeds $15 billion globally) are prescribed with very few data available to identify individuals who would be most likely to benefit, and thus those in whom the therapies will be cost-effective.\(^12\) The introduction of “data liquidity”\(^14\) with custom IT systems in neurology accelerates the translation of research to the clinic and beyond. It may even integrate data collected directly from patients.\(^15\) The convergence of large curated data sets mined by complex systems through applied statistical techniques has the potential to transform the assessment of the patient, providing highly sophisticated tools to give clinicians new insights on the patient’s condition—past, present, and future—and inform decision making at the point of care.

To address current limitations and advance translational opportunities to improve MS research and care, we have developed the MS BioScreen application. The MS BioScreen is a tablet-based navigation system tailored to an individual patient and coupled with a secure, powerful, cloud-based database infrastructure that integrates multiple dimensions of disease information: clinical evolution; therapeutic interventions; brain, eye, and spinal cord imaging; environmental exposures; genomics; and biomarker data. The initial prototype was based on a comprehensive prospectively ascertained database of >600 MS patients with 10-year follow-up, with additional data sets added for confirmation and to augment the power of the tool. Here, we introduce the prototype and discuss 3 key evolutionary phases in its deployment: the display (accessing data), contextualization (understanding the data), and actionable interpretation (using the data to assist decision making).

Attributes of the Prototype

Core Data Set

An extensive multicomponent longitudinal data set, the University of California, San Francisco (UCSF) MS-EPIC cohort (Multiple Sclerosis Epigenetics, Proteomics, Imaging, Clinical; http://msepicstudy.com/), is the foundation of the project. The EPIC study spans the heterogeneity of the disease, with enriched sampling on the first decade of the disease course, to capture changes in disability and conversion between clinical states. The UCSF Committee on Human Research approved all components of the EPIC study, including development and deployment of the BioScreen application.

The MS BioScreen Architecture: Tablet Application and Data Infrastructure

The project is conceived as an integrated software toolkit for organized data access and visualization. The front end
enables an intuitive and actionable interaction with the data, stored remotely on file servers that can manage terabytes of data, including high-resolution image data for brain spinal cord and the visual system. The data are securely accessed via an application programming interface, developed for BioScreen, which can retrieve in real time relevant information at the individual patient level and gather data aggregated from groups of patients with similar features, such as age at evaluation, age at disease onset, treatment history, imaging, genetics, and other variables.

**Beta Testing and Early Assumptions**

This first iteration of the application is currently being deployed in early field testing. User feedback from the beta-tested prototype is then used in an iterative fashion to inform subsequent phases of development. Clinicians have been asked to comment on their experience imme-

![Image](image.png)

**FIGURE 1:** Multiple sclerosis (MS) BioScreen prototype application. An image capture from the overview screen illustrates an individual patient’s data presented in anonymous mode. The initial layer of the application is a visualization of an individual’s overall health information, providing a gateway to the full complement of accessible data. This view introduces the defining characteristics of the patient and the disease course: name, gender, age, disease onset, disease course, duration, and relapses on the top bar. It is otherwise organized by data type, with clinical information (clinical presentation over time, treatments, and attacks) displayed in the panels on the right, and imaging and biomarker data (including MS genetic risk markers) on the left. EDSS = Expanded Disability Status Scale; INF-β = Interferon Beta; IVSM = Intravenous Solumedrol; T2LL = T2 Lesion Load; MSGB = Multiple Sclerosis Genetic Burden. Copyright, Regents of the University of California; all rights reserved.

diately after using the application. Similarly, patients have provided feedback on the application through an anonymous online survey in which they are encouraged to share their impressions and suggest improvements to the tool. The current beta-testing protocol addresses the consumer-friendliness of the application and its user interface, and confirms or challenges the assumptions underlying its design from real-life interactions with a diverse user group.

**Developing a New Perspective on an Individual Patient**

As shown in Figure 1, the patient overview screen is a visualization of an individual’s overall disease status, providing a gateway to the full array of accessible data, including baseline metrics, relapse history, treatment data, imaging (both the original images and automated quantitative assessments), genomic data, and biomarkers. This view introduces the defining characteristics of the
Contextualization of Individual Data Using Population-Based Evidence

Contextualizing refers to the display of an individual subject’s data in relation to a customizable reference population, enabling a direct normative evaluation of the individual subject’s trajectory. Contextualization may assist the interpretation of any type of assessment. As examples, in Figure 4, a quantitative assessment of the patient’s whole brain volume change over time, compared with that of the reference population, is visualized, and in Figure 5 the patient’s year-to-year change in clinical impairment (in blue) is summarized for a widely employed outcome measure for MS, the Extended Disability Status Scale (EDSS). In both figures, the individual’s data points are displayed in the context of a population-based percentile distribution (orange) derived from patients with similar characteristics (bottom menu bar). This reference population is accessible at all times, and can be selected with an automated algorithm, or manually edited to refine the comparison using simple filters. Enabling a multidimensional comparison between the trajectory of an individual patient and those of similar individuals from the reference database can provide immense immediate value to both the clinician and patient. Contextualization fosters an unambiguous
understanding of an individual’s unique disease profile relative to others in a clear and simple manner, and by doing so supports education, promotes communication, and encourages collaborative decision making. Various types of biomarker information, including genetic risk variants for MS, can also be displayed (Fig 6). An individual’s loading for these risk variants is summarized by comparison to its distribution in reference groups.

**Anticipating Outcomes**

Meaningful advances in decision support will require tools that can anticipate a patient’s future disease evolution, based on his or her data combined with information from other patients with similar trajectories but longer follow-up. The current version of the application addresses variability in 2 ways: by displaying the percentile line of the distribution and by providing filters to refine the characteristics of the reference population.
More refined automated algorithms are needed to better quantify the comparisons, and to define optimal filter parameters to predict outcomes. In Figure 5, on the right side of the screen a prediction of EDSS 1 year into the future was generated using a prototype program under the assumption that current therapy (natalizumab) would be continued. The predictive display illustrated in the figure represents only a preliminary example of what is possible with the application; it is based on a small number of reference patients and has not been validated prospectively in a real-life clinical situation. The development of predictive algorithms that are useful at an individual level will require, foremost, access to additional robust reference data sets that capture the full diversity of individual trajectories and treatment scenarios in MS.

**Adoption Drivers by Patients and Clinicians**

Ten clinicians, all specialists in MS care at our institution, have used the application with patients in an outpatient clinical environment. They were uniformly enthusiastic, reporting that the BioScreen provides them with a new perspective on the individual patient’s disease, based on the visualization of real data. These simple features are also perceived as substantial time-savers, improving communication and education and promoting shared decision making with patients. We have also initiated a survey to evaluate the level of comfort that participating patients have for the BioScreen tool. The feedback validates many of the assumptions underlying the tool; 96% of 364 patients indicated an interest in gaining access to their own data, including 91% for their research data. They were comfortable with a model of online access via a secure application (93%), and the vast majority offered to contribute their own individual anonymized data to the assessment tool (89%).

**The Powerful Combination of Data and Software Tools**

The MS BioScreen enables the clinician to track an individual patient over time and compare the individual’s trajectory to that of a reference group of similar patients.
Practical and user-friendly, the BioScreen embodies a new way to leverage complex data sets, recognize patterns, and interrogate specific features with prognostic significance. It amplifies the physician’s expertise and provides an evidence-based, data-driven, custom-made context to each patient’s unique MS experience. Supported by evidence from patients and clinicians, we have gone through 3 phases in the development of a powerful precision medicine tool: (1) visualization of individual data, (2) contextualization of information using cohort populations, and (3) decision support features. The BioScreen enables progressive learning and refinement of contextualization and prediction algorithms, bridging data from multiple contexts. As a 2-way communication tool, the BioScreen brings multidimensional information to the point of care and in turn can serve as a way to identify novel research questions arising from the point of care. By providing perspective on a single individual based upon comparison to a reference population, the BioScreen enables researchers to look at population data in novel ways, identify extreme outliers, and stratify subgroups of people based upon disease course, imaging, genomic, and/or biomarker characteristics.

Blurring the Frontier between Research and Clinic: Big Data in Health

The application’s value ultimately depends upon the accuracy of the computing algorithms combined with the quality of the data sets, defined in terms of number of patients, comprehensiveness of the information available, standardization, transferability to different clinical environments, and coverage of the disease timeline. It is not surprising that this new tool emanated initially from research, especially genetics research; whole genome sequencing, for example, not only is intrinsically “personal by nature” but has some interesting sustainability aspects, because the yet-to-be-discovered genetic factors associated with conditions can be extracted from the data set years after the data was produced.

Far from challenging the expertise of clinicians, precision medicine tools are envisioned only to amplify the clinicians’ role, enabling new insights while promoting communication of complex information in succinct, quantitative, actionable ways. Although new technology certainly exists to enable the capture, protection, transfer, and interpretation of data from multiple sources, research
institutions will need to mitigate the friction between the high-depth, low-sample data model and the fast-growing customer-based model by forging unprecedented partnerships.

**Precision Medicine and the Future of Collaborative Care**

The emerging field of precision medicine opens exciting opportunities to deliver more precise, evidence-based, and collaborative medical care. Precision medicine is built on the absolute requirement of a high-quality data set. Beyond genomics, and building on the early promising foray of “personalized” medicine into cancer treatment, other chronic medical conditions are also likely to benefit from these transformative new technologies. From the patient’s point of view, there is emotional and financial urgency in finding the right treatment, and this urgency creates new opportunities for care and care collaboration. In the MS BioScreen model, a more transparent understanding of the disease can lead to a more active role in decision making, consistent with the growing trends of patient empowerment. Another potential dimension to the BioScreen could be to superimpose economic data to enable patients to evaluate the physician’s recommendations, and elect and preauthorize the treatment that will be most sustainable for them. Greater involvement of patients at the time of therapeutic decision making translates into greater compliance with treatment, which is linked to higher efficacy and lower healthcare costs. Ultimately, all patients would have the option of interrogating their own data interpreted in the context of the world’s largest reference cohort and the latest data on available therapeutic options. It is likely that some patients will wish to play an active role in their own health management with these personalized disease management tools, whereas others will prefer to delegate decision making to their clinicians. Down the road, there seems little doubt that the health care industry will be gradually transformed by “digital consumerism.” Access to—and exchange of—specific information equips the patient to be an active member of the health care team, by entering data (including data from portable

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**FIGURE 6: Display of biomarker information and contextualized representation of aggregated genetic risk scores.** The left panel shows current values for various types of laboratory and biomarker information relevant to multiple sclerosis (MS), including: typing for the disease-associated HLA-DRB1*15:01 allele, value of the Multiple Sclerosis Genetic Burden Score (MSGB) with and without the contribution of the major histocompatibility complex region, vitamin D3, vitamin B12, TOB1 gene expression, and cerebrospinal fluid analyses. In the right panel, the MSGB score was computed based on a weighted scoring algorithm using independent 64 single nucleotide polymorphisms associated with MS risk. Similarly to Figures 4 and 5, the orange boxplot displays the 5th, 25th, 50th, 75th, and 95th percentiles of the distribution of the score in the reference population indicated in the bottom blue bar. The application is displayed in anonymous mode. MSGB = Multiple Sclerosis Genetic Burden; MHC = Major Histocompatibility Complex; SNP = Single-Nucleotide Polymorphism; Tob1 = Transducer of ERBB2, 1; CSF = Cerebrospinal Fluid; MNC = Mononuclear Cell; IgG = Immunoglobulin G; OCB = Oligoclonal Bands. Copyright, Regents of the University of California; all rights reserved.
biosensors) useful in the management of the condition, recording/tracking notable events and day-to-day care, and providing a much more granular, continuous perspective on the disease and its progression. This participation will lead the way to a more complete understanding of the impact of the condition across more diverse domains than could ever be inferred from traditional (brief and infrequent) clinical assessments.

**Perspectives**

Several social and ethical questions are emerging from data-driven interactions inherent in the development of personalized medicine. Skeptics assert that personalized medical applications have not yet proven to fulfill their promise of providing direct benefit for patients. At least, visualization tools assure that data can be communicated to patients with better precision, especially if supported by educational materials adapted for users at different levels of sophistication. Another objection is based on concerns that the apparent power of numbers could cause both patients and clinicians to defer their choices to algorithms. Yet even if artificially intelligent systems can provide computed insights unattainable by a human, deeply human traits will need to be factored in, such as tolerance for risk, perception of being lucky or unlucky, grading the seriousness of a particular disability or limitation, or even capacity to analyze the nuances of a complex series of options. All of these factors, often perceived subconsciously, profoundly influence how personal health care decisions are made, as well as how options are communicated to patients by clinicians. The availability of objective clinical information assessing an individual's disease trajectory, plus a capacity to predict the probability of future outcomes based upon decisions implemented today, amplify the expert's role by helping to focus the clinical interaction in a precise, patient-centric manner. By providing a new level of sophistication, the BioScreen provides ready access to data from multiple sources to promote efficient, informed, personalized, and precise decision making in a way that can empower both patients and clinicians and recast the management of patients with chronic conditions.

**Authors Note: Availability of the BioScreen**

The BioScreen has been trademarked by UCSF. Additional MS cohorts from collaborating academic institutions are currently in the process of being incorporated into the reference data set to improve contextualization and predictive capabilities of the device. Following approval of appropriate regulatory agencies, we intend to make the BioScreen available to clinicians and patients worldwide.

**Acknowledgment**

This work was supported through a Patient-Centered Outcomes Research Institute (PCORI) Pilot Project Program Award (IP2PI000609), the NIH National Institute of Neurological Disorders and Stroke (R01 NS049477), the National Multiple Sclerosis Society (RG 2899-D11), the Conrad Hilton Foundation, the UCSF Precision Medicine Initiative, a UCSF CTSI Catalyst Award, and the NIH National Center for Advancing Translational Sciences (award number KL2TR000143; J.M.G.). P.-A.G. is a recipient of the Race to Erase MS Young Investigator Award. S.E.B. is a Harry Weaver Neuroscience Fellow of the National Multiple Sclerosis Society.

We thank previous investigators of the UCSF MS-EPIC cohort, the PCORI-initiated stakeholder’s advisory board of the MS BioScreen, the staff who contributed to the cohort, and especially our patients who entrusted us with the use of their personal medical information for research.

All statements in this report, including its findings and conclusions, are solely those of the authors and do not necessarily represent the views of PCORI, its Board of Governors, or its Methodology Committee.

**Authorship**

P.-A.G. and S.L.H. led the project and were the primary authors of the manuscript. R.G.H., B.A.C.C., J.C.C., A.L.,

Potential Conflicts of Interest

B.A.C.C.: consultancy, Abbvie, Biogen Idec, EMD Serono, Genzyme/Sanoﬁ-Aventis, MedImmune, Novartis, Teva Neurosciences; contracted research support (including clinical trials), Acorda, Avanir, Biogen Idec, EMD Serono, Hoffman–La Roche, Novartis. J.M.G.: medical legal consulting related to CNS inﬂammatory disease. J.S.G.: consultancy, EMD-Serono. A.J.G.: served on committees for studies sponsored by Biogen Idec, MedImmune, Novartis; consultancy, Mylan Pharma, Novartis, Accorda, Prana Pharma, Roche; expert witness, Mylan Pharma; scientiﬁc advisory board, Bionure, Inception 5; founder, Inception 5; grant, Novartis. H.-C.v.B.: grants, Pfizer, Roche, Genzyme; personal fees, Novartis. S.S.Z.: honoraria for speaking engagements, Teva Pharmaceuticals, Biogen Idec, Genzyme, Novartis, EMD-Serono, Questcor, Roche; data safety monitoring board, Lilly, BioMS, Teva, Opera Therapeutics. E.C.-H.: consultancy, Teva Neurosciences, Biogen Idec, Novartis. S.L.H.: scientiﬁc advisory board member (retired), BioMarin, Receptos; scientiﬁc advisory board member (if company is funded), Symbiotix, Annexon, Bionure; stock/stock options, Receptos (transferred to University of California regents).

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