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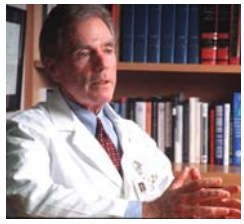
Prospective medicine: the role for genomics in personalized health planning



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> 'We believe that genomics and pharmacogenomics are necessary pieces of a broader shift in focus for healthcare'

A wounded healthcare system

The US system of healthcare is rooted in a short-term focus on treatment of disease, rather than quality-of-life enhancement through prevention of chronic illness. With a US$1.5 trillion price tag last year [1], US healthcare costs accounted for 14.1% of the gross domestic product. These figures are expected to grow to US$2.8 trillion and 17.7% by 2011 if American medicine continues on its current path [2]. With uncontrolled costs, inefficiency and lack of satisfaction on the part of consumers or providers, our healthcare system is in danger of collapse. In the last decade, expenditure on chronic disease has grown to almost three-quarters of US healthcare spending [201]. Although medicine is currently preoccupied with late-stage treatment of high prevalence diseases, a coherent emphasis on practicing prospective care to avoid or reduce disease could help cure some of healthcare's maladies.

Our healthcare system does not yet effectively customize 'one-size-fits-all' therapeutic regimens for a patient's specific disease phenotype. However, technologies emerging from the fields of genomics, proteomics, metabolomics and bioinformatics are now making it possible to distinguish amongst phenotypes that have been considered as one nominal condition [3,4]. Many experts have suggested that genomics and pharmacogenomics will transform medicine and drug development [5,6]. Others have argued that many current genomic tools are more hype than substance, and that decades will be needed before genomics has a significant impact on healthcare [7,8]. We believe that genomics and pharmacogenomics are necessary pieces of a broader shift in focus for healthcare, from inconsistent reactive diagnosis and nonspecific disease treatment, to standardized prospective assessment, personalized health planning, and selective individual treatment.

We predict that accurate prospective risk assessment tools will be developed to help guide physicians and patients to prevent unnecessary illness [9]. To facilitate rational care, providers, medical centers, patients, insurers, policy makers, and medical therapeutics companies should work to integrate systems in order to create quantitative predictive modeling tools and deliver effective personalized healthcare. Cogent tailoring of not only drugs but the entire health plan to the individual will enhance compliance, minimize side effects and optimize disease prevention efficacy.

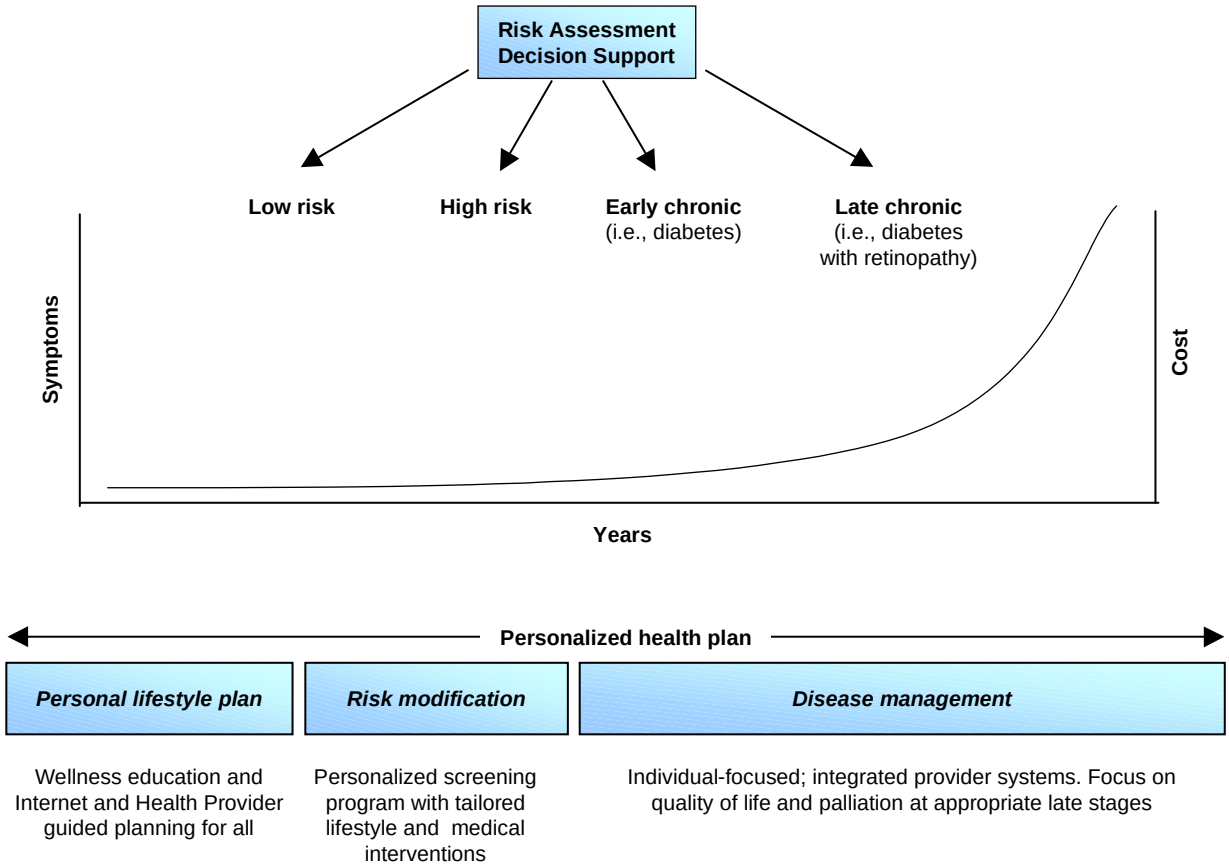
A case in point is obesity, which greatly increases risk for a number of serious diseases, and cost the US an estimated US$100 billion last year [202,203]. The major causes of the rapid rise in this condition are the social changes since the 1970s that have decreased physical activity and increased caloric intake; 30% of Americans are now obese and 64% are overweight [204]. Since the environmental causes of obesity are well characterized, it is reasonable to integrate broad-based healthy lifestyle initiatives into medicine today.

However, that is not enough. There is increasing data that multiple etiologies of obesity have a significant genetic basis. Genomics will help provide more specific approaches to prevention and treatment for such individuals. For example, mutations in the melanocortin-4 receptor (MC4R) are the commonest known monogenic cause to date, implicated in 1–6% of early onset or severe adult obesity cases [10,11]. Agonists that bind MC4R reduce food consumption and weight in obese model organisms; hopefully, appropriate versions of these drugs will help people with various MC4R mutations who suffer from binge eating disorders [12-15]. A pharmacogenomic approach alongside personalized lifestyle recommendations and motivation techniques may be the best solution for addressing obesity primarily due to variations in genes related to metabolism and the neural control of hunger and satiety.

Prospective risk assessment and personalized health planning

In any population, individuals may be at low or high risk for a given disease, or already in a state of chronic illness (Figure 1). The goal of

Figure 1. Prospective healthcare.



Current medical care is reactive. Prospective Risk Assessment Decision Support will predict likely future disease inflection points, while Personalized Health Planning will prevent or delay illness, increasing quality of life, and improving cost-effectiveness.

prospective care is to quantify risk and/or detect disease at its earliest onset, when there is an effective intervention available that reduces morbidity or mortality. Currently, skilled physicians can collect and use history and physical examination data to prospectively approximate risk on a rather subjective basis. This guides selection of laboratory tests, imaging and other diagnostic tools to further assess the patient's stage of health or risk for different diseases. However, these sporadic and qualitative 'risk assessments' generally encompass only a few diseases and are greatly limited by a lack of quantitative data and a particular doctor's experience, memory, and time. Physicians are overwhelmed by competing sources of unorganized new information. They are also forced to see too many patients in too short a time to get to know them well enough to develop more than a cursory assessment, let alone to design a health plan.

It is critical that we move to a 'Prospective Health System' that predicts and prevents disease, thus improving patient care, physician satisfaction and healthcare economics. Such a system would expand the limits of primary prevention forecasting accuracy, and ensure more equitable access to optimal primary and secondary preventive care. Since Wilson and Jungner's 1968 World Health Organization report on the principles of population-based screening [16], detection methods for hundreds of diseases have been developed [205-207]. For example, the discovery of overly elevated fasting glucose and hemoglobin A1C, allowing intervention for early-stage diabetes, can delay or prevent the onset of late-stage complications, such as retinopathy, neuropathy, nephropathy and cardiovascular disease [17]. Even without genomics and other advanced diagnostics, comprehensive prospective care models already exist for diseases

other than diabetes, such as congestive heart failure [18-20], and asthma [21]. Genomics, imaging, and other medical technologies will further enhance diagnostic forecasting power, allowing the prediction of more diseases before the onset of noticeable symptoms [22].

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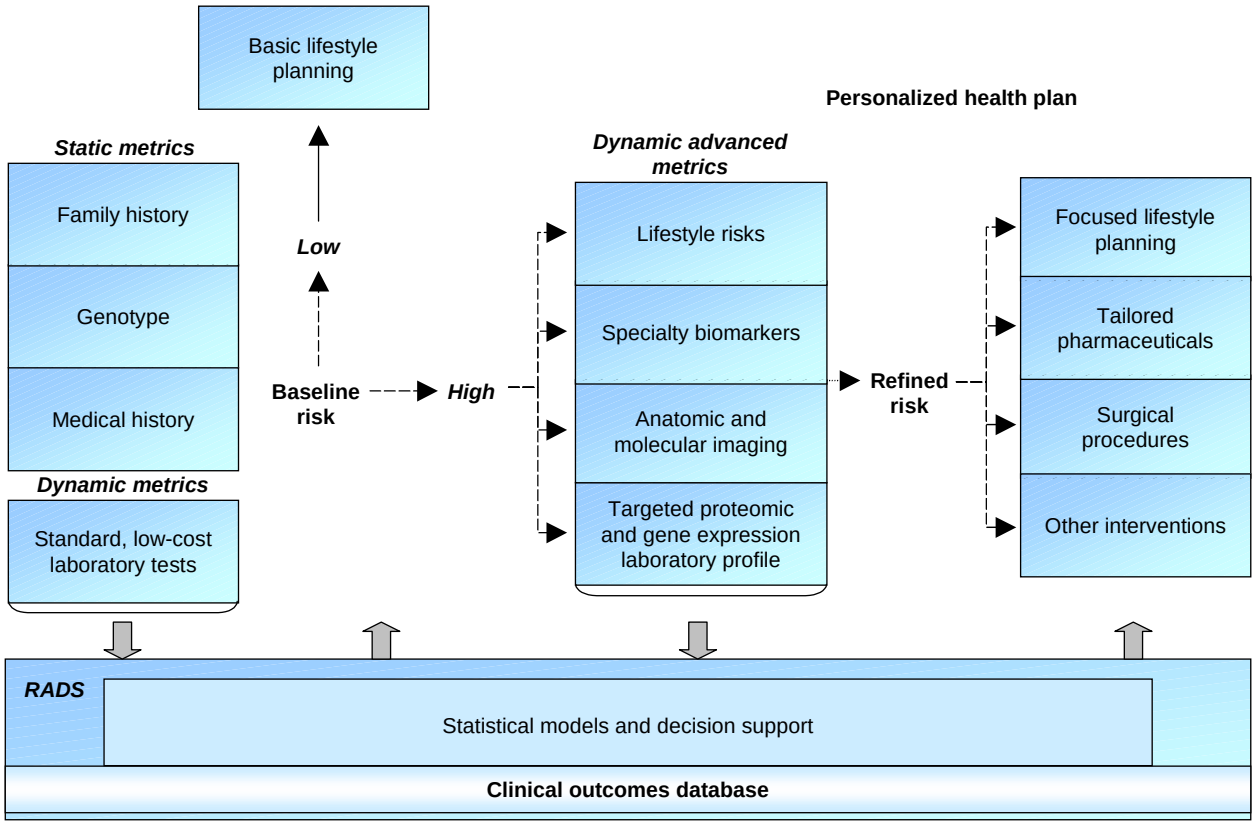
An important question is: why have broad prospective and personalized approaches to healthcare not taken hold? For one, individualized risk assessment tools are not generally available to help physicians ascribe risk and conduct appropriate screening tests. Furthermore, medical schools have not effectively taught prospective approaches, and reimbursement systems actually retard their development and use. Long-term changes could be achieved through amendments to the International Classification of Diseases (ICD) and Current Procedural Terminology (CPT), as well as a new emphasis on prospecive and personalization methods in key clinical and scientific publications and stakeholder agendas. A functional prospective health system that provides consistent and equitable patient access and care would reward healthcare providers for use of scientifically up-to-date, evidence-based Risk Assessment Decision Support (RADS) tools, and best-practice screenings for preventable diseases. It would also reassure payors by utilizing the RADS tools to quantify expected cost savings of prospective interventions, more accurately than current population-based actuarial methods.

Initial risk probabilities for an individual would be derived from 'static' data, such as family history, genotype, and past medical history. This baseline risk would be updated throughout life by new family and medical data, and be complemented by standard laboratory data and diagnostics. In the near future, new technologies and clinical information will refine predictability and inform selection of appropriate advanced screening tests and their frequency of use. Ongoing standard (i.e., cholesterol) and advanced screening (i.e., gene expression, molecular imaging) tests of an individual's dynamic pathophysiology will allow for more accurate prediction of that person's likelihood of disease development in the near-term (Figure 2). For example, screening for colorectal cancer is currently recommended for all people aged > 50 years, based on its average age of development in the population [23]. Yet we have seen the rate of this disease rise in young adults [24]. We could save lives and money by screening individuals with calculated high risk more often and by beginning at a younger age.

To accurately predict timing of disease development with and without intervention, patient information will need to be compared to large, anonymous knowledge banks of genomic information and clinical outcomes. Such back-end databases would ideally be updated regularly and reviewed to ensure population diversity and scientific legitimacy. Methods that facilitate these attributes will add greatly to the accuracy and relevance of a RADS approach. A wealth of open source information about the human genotype and disease genes is available [208,209]. Large amounts of clinical outcomes data also exist in both the non-profit (i.e., Framingham Heart Study) and for-profit (i.e., Myriad Genetics) realm but are disparate and typically not as accessible as human genome information due to individual patient privacy concerns [25,210-214]. Intelligent and ethical methods for utilizing as much data as possible in tandem will increase the accuracy and utility of a RADS tool.

Statistical modeling methods would be used to compare the patient information to the clinical outcomes data, in order to predict risk and the preventive value of different interventions, over a number of future time points. Current predictive modeling software uses a combination of logistic regression and/or neural networks (artificial intelligence), but the accuracy of current tools needs to be honed. Improved statistical algorithms, expanded data sets to better reflect different populations, and more frequent updates with new clinical outcomes data and science will be critical. Furthermore, we hope that future applications will address more diseases, and provide detailed screening and intervention decision support [26-31,101]. To operate most efficiently within the physician's work flow, we project that a RADS tool would evaluate patient information entered and stored in an Electronic Medical Record (EMR). Hopefully, the development of a standardized EMR model by Health and Human Services and its partners will

Figure 2. Risk Assessment Decision Support.



Genotype/family history data, medical history and standard low-cost laboratory tests provide a baseline risk assessment. This data guides customized advanced diagnostic screening to provide a more accurate risk assessment, where indicated. Given the degree of refined risk, tailored plans would provide options ranging from focused lifestyle planning through to more intensive forms of intervention.
RADS: Risk Assessment Decision Support.

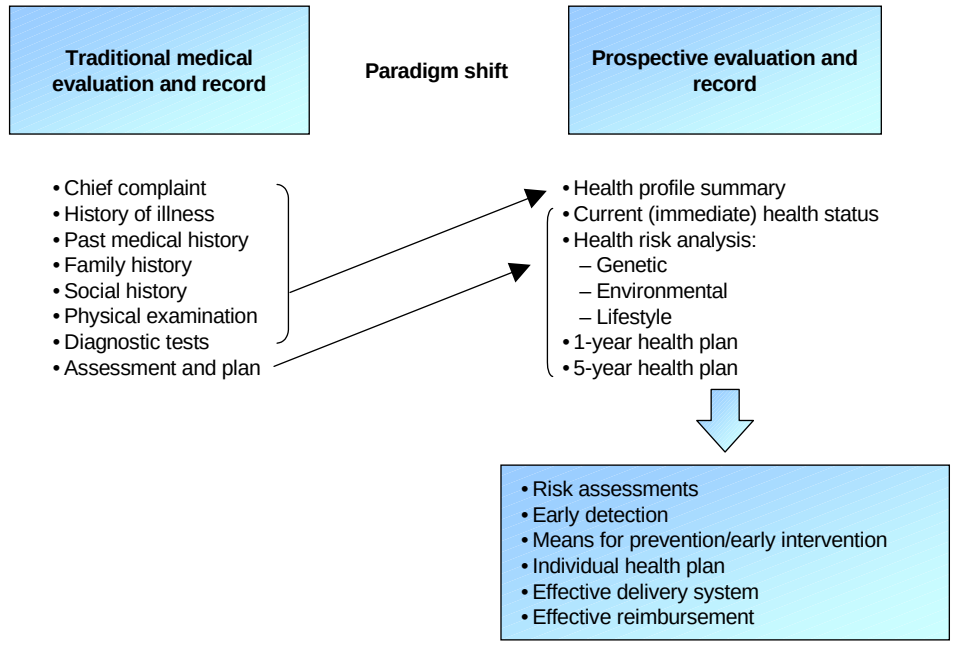
provide a common platform for which to develop a secure RADS tool [215].

Although the patient motivation value of risk assessments is unclear [32], the potential value is high for focusing physician efforts on the unique screening and intervention needs of individuals. Medicine is already beginning to recognize many more categories of individual variations on disease given differing genetic backgrounds and environmental influences. Hopefully, the field of pharmacogenomics will be responsive, allowing doctors to prescribe the most appropriate interventions possible. Furthermore, organization of prevention recommendations into personalized health plans would help patients make the best use of their risk assessments (Figure 3). The lack of sufficient health planning is reflected in the low compliance of patients with lifestyle and pharmaceutical interventions, with medication non-adherence typically in the range of 30–60% [33]. In our opinion, tailoring materials and providing a clear plan to the individual, along with personal and electronic support systems, will increase compliance with appropriate intervention strategies [34].

Phasing genomics and pharmacogenomics into health planning

Isolated individual genetic and biomarker tests are already making a significant impact on the quality of medical care. Tests to distinguish cancer severity and risk (i.e., *BRCA1* and *BRCA2* in breast cancer), and to optimize cancer therapies (i.e., 6-mercaptopurine dosing for acute lymphocytic leukemia) are becoming more common in practice today. Pharmacogenetic tests to optimize drug selection and dosing are also already in use for cardiovascular diseases, depressive disorders, asthma, pain, and anesthesia [35,36].

Figure 3. Paradigm shift.



In a Prospective Health System, the focus of the healthcare team would shift to developing a stronger relationship with individual patients, and an extensive, proactive and personalized health plan.

Debilitating monogenic diseases have been easier to pinpoint and create interventions for than the more common, chronic multi-gene disorders. Variable and growing state-supported newborn screening programs have been in place in the US since the early 1960s. Beginning in 1997, Duke, Neo Gen Screening (now Pediatrix), and the State of North Carolina piloted tandem mass spectrometry screening of newborns for a broad range of monogenic metabolic diseases detectable after birth; this process was adopted as a state requirement in 1999. From 1999 to 2002, only one metabolic disease in every 4400 infants was detected, and mortality was reduced to zero [37,38]. Tandem mass spectrometry and extensive newborn screening is currently implemented in 21 states [216], and organizations like the March of Dimes and Centers for Disease Control are reviewing genomic and proteomic methods as they attempt to design cost-effective recommendations for national standards [39].

Using genetic information to predict and intervene against risk for monogenic or highly penetrant familial disorders, such as hereditary hemochromatosis, has proven useful for some adult patients but its value is still being questioned [40]. Furthermore, it has been more difficult to collect genomic information to quantify risk for chronic multi-gene disorders. Thus, it is of concern that some early genomic 'solutions' for particular conditions are being rapidly rolled out to predict appropriate lifestyle habits but have unsubstantiated value and questionable cost-effectiveness [41].

On the other hand, a gene expression microarray chip for the cytochrome P450 (CYP) metabolism genes *CYP2D6* and *CYP2C19* might effectively aid physicians in assessing genetic susceptibilities to toxicity from a wide range of drugs. Polymorphisms detected in these two enzymes can affect the rate at which an individual metabolizes up to 25% of drugs on the market, including those used to treat cardiovascular disease, high blood pressure, depression, and attention deficit hyperactivity disorder (ADHD) [217,218]. Thus, a single test could inform numerous drug dosing decisions over the life of the patient. The National Center for Toxicogenomics also created a ToxChip, which is used for toxicology research studies today but may be used for individualized environmental toxicology assessments in the future [42]. Disease-specific chips are also under development for cystic fibrosis, HIV-1 resistance, p53-related cancer, colorectal cancer, and human papilloma virus infection [219].

By giving dynamic gene expression information, the 'chip' and proteomic approaches to single diseases will enhance the ability to predict risk and timing of future disease, allowing for more appropriate prescriptions. Chips could also be used to help calculate baseline risk by providing genotype data. Focusing on only one or a few diseases at a time might be more comfortable for individuals and society, than whole-genome profiling. On the other hand, this focus on single-disease profiling, rather than looking at the whole person, may minimize the prospective and cost-saving opportunities for healthcare.

'We suggest that 'non-treatable' patient information should generally remain undeclared, until new scientific data provides an opportunity to intervene and reduce risk'

Guttmacher and Collins of the National Human Genome Research Institute (NHGRI) have noted that within the next decade or two it will be possible to sequence a person's entire genome for < US$1000 [43]. An article in *Science* forecasted that: 'Shortly after a person is born, her genotype is recorded at her physician's office… Assisted by a decision support system, her physician may prescribe a personal immunization and screening schedule or recommend specific preventative measures' [44]. If privacy could truly be ensured by security technology, perhaps the ultimate aim for health system efficiency would be to sequence one's genome at birth, compare it to known polymorphisms associated with environmental susceptibilities (including drug toxicities), and store that information in a standardized and confidential EMR for comparison with human genomics and clinical outcomes databases. Science is making a great deal possible but social issues may limit adoption for quite some time.

Ethical considerations and Heath Information Portability and Accountability Act (HIPAA) requirements make protection of an individual's records, genomic or otherwise, a requisite element before a RADS program could be put in use. Whether or not risks for which there are no effective interventions should be reported to the physician and the patient is an important ethical question to be carefully considered. We suggest that 'non-treatable' patient information should generally remain undeclared, until new scientific data provides an opportunity to intervene and reduce risk.

'We believe that personalized care will be the future of medicine, and genomics will play an enabling role...but healthcare delivery must be redirected to incorporate prospective approaches'

Industry, research, and development

The largest pharmaceutical industry players have targeted diseases with high prevalence as part of the 'blockbuster' strategy, in order to get the highest possible returns on development costs, over the life of a drug's patent. As a result, the top ten pharmaceutical companies went from earning US$200 billion in 1990 to US$1 trillion in 2000. But drug discovery has recently progressed slower than expected, and drug development costs have increased 2.5-fold in 10 years to US$800 million per drug. This factor, on top of the already high cost of drugs, will inevitably force changes in the practices of the industry [45].

Companies like Genzyme are now effectively creating and licensing discoveries for smaller population diseases, while Genentech is benefiting from a smaller market approach with the success of a monoclonal antibody, which is useful in only Her-2-positive breast cancer. We predict that pharmacogenomic advances will make this targeted 'niche-markets' approach the wave of the future, by facilitating more directed and cost-effective clinical trials, and the development of more efficacious drugs that will increase customer satisfaction and prescription compliance. Investments in public efforts, such as the NIH Roadmap small molecule library and NHGRI projects; multidisciplinary academic programs, such as the Duke Institute for Genome Sciences and Policy; industry partnerships, like the SNP consortium; and multi-pronged, non-profit initiatives, such as the J Craig Venter Science Foundation (JCVSF), should make this prediction a reality [209,220-222].

We believe that personalized care will be the future of medicine, and genomics will play an important enabling role. For this to happen, however, the healthcare delivery system must be redirected to incorporate prospective approaches. At present, the barriers are both technical and social,

and we suspect the latter may be the greater obstacle, but hope they will be overcome by debates regarding the definitions, legal issues and ethics surrounding genomics and medical information flows [46,223,224]. Cautiously unleashing the predictive power of genomics and medicine will help facilitate a needed transformation in the quality and economics of healthcare.

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