White Paper on Unmet Medical Needs and Challenges

"Is it Working? Individualizing Medical Therapy Through Rigorous Symptom Monitoring Using Smartphones"

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Medical drugs and devices are approved by the Food and Drug Administration based on demonstration of safety and effectiveness in adequate clinical studies. However, many FDA approved treatments that are effective on average do not work (or provoke unacceptable side effects) in a large minority of patients. And in the context of comparative effectiveness research, a treatment that is superior on average may be inferior in select individuals. As described by our research group, heterogeneity of treatment effects (HTE) arises from individual differences in disease severity (risk), responsiveness to treatment, vulnerability to adverse effects, and utility for various outcomes (Kravitz, Duan, Braslow 2004). HTE can be large. In one well-documented example, Rothwell showed that among candidates for carotid endarterectomy, the absolute benefit (risk reduction with surgery) ranged from 14.1% for patients at high risk for stroke without surgery compared with -1.4% for patients at low risk (Rothwell 1995). Another important demonstration of HTE occurred within the STAR*D trial, which showed that less than one-third of patients with major depression responded to the first drug prescribed; only with considerable effort (switching to other antidepressants, augmentation with bupropion, or both) were some 60-70% of patients able to achieve durable remissions (Rush 2007).

Clinicians and patients recognize HTE and deal with it in various ways, most often through a series of informed (but informal) therapeutic trials: the physician prescribes treatment, reassesses the patient weeks to months later, and decides whether to continue the treatment, switch to another, or stop altogether. This approach works reasonably well for conditions in which there is a readily available, reliable, and clinically valid physiological or biochemical "test" – e.g. blood pressure for patients with hypertension or LDL cholesterol for patients with dyslipidemia. But for the many conditions in which the aim is to ameliorate *symptoms*, the physician is often left to make treatment recommendations based on the patient's response to one or two questions. (E.g., "How are you doing? Do you think the medicine is helping?") Unfortunately, this informal approach lacks rigor and may result in patients taking drugs for months or years that provide no discernible benefit. A more rigorous approach would be to enroll patients in an "n-of-1" clinical trial – a single patient crossover trial in which *concealed* Treatments A and B are *randomly assigned* for fixed time periods, and outcomes assessed using *patient-centered, standardized measures* at pre-defined intervals (Kravitz, Duan, White 2008). However, for reasons advanced elsewhere, n-of-1 trials have not enjoyed widespread uptake (Kravitz et. al 2009).

The challenge, therefore, is to introduce some of the rigor of n-of-1 trials into practice. Concealment and randomization may not be feasible, but use of patient-centered, standardized measures to monitor symptoms is potentially game-changing. The need is for fun, easy-to-use applications for handheld devices (such as smartphones) that can collect and store information on symptom status at much shorter intervals than is usually possible in routine care. For example, an application for migraine patients could "beep" and ask about headache symptoms at the end of each day. Then at a subsequent office visit, physician and patient could view the information graphically in relation to recent changes in therapy.

While designed to enhance clinical care, such applications could also have relevance to clinical research. Over time, clinicians could compile large databases of patient-centered outcomes in relation to treatment. Using Bayesian statistical techniques, these databases could be combined with evidence from RCTs to design individually tailored treatment programs, enhancing the probability of initial treatment success. (Hay et al. 2008)

References

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