The digital phenotype of vaccination

To the Editor — Vaccines against COVID-19 have been a remarkable public health success. However, as with all vaccines, immunologic response can vary by several orders of magnitude between individuals[1]. This is important since antibody levels following COVID-19 vaccination have been shown to correlate with the level of protection[2]. As only a miniscule fraction of the over 5 billion people vaccinated worldwide have undergone blood testing to analyze their immune response, for the majority of people the ultimate measure of their adequacy of immune protection is whether they experience a breakthrough infection and the level of its severity.

Vaccination activates the innate immune system, triggering the synthesis of inflammatory cytokines critical to launching an antigen-specific adaptive immune response. The physical manifestations of this inflammation, termed reactogenicity, has historically been tracked only by symptom surveys. Limited studies directly measuring inflammatory blood biomarkers have not only found substantial inter-individual variation in this inflammatory response, but also a strong correlation between this response and both systemic symptoms[3] and humoral immune reponse[4].

Systemic inflammation, even at low levels, can manifest as subtle but measurable physiological changes in multiple parameters, including temperature, heart rate, blood pressure and heart rate variability[5]. Because of the normal variation in these parameters that a person experiences throughout each day, as well as day-to-day, potentially meaningful changes can go undetected through occasional spot checks. Furthermore, due to the substantially large inter-individual differences, population-based cut-offs, such as a temperature of >38 °C, are especially insensitive. Because wearable sensors can now continuously track multiple physiological and behavioral parameters, we have, for the first time, the ability to detect these small individual changes and objective measures of reactogenicity.

Early proof-of-concept data from the DETECT[6] study and from other studies[7–9] confirm that consumer wearable sensors can detect the individual physiological and behavioral changes associated with the vaccination and the consequent inflammation. All three studies[7–9] identified significant post-vaccine changes in daily summary values of physiological and behavioral parameters relative to their pre-vaccine individual baselines. The level of deviation from normal was moderate. For example, a mean increase of only 1.5 beats per minute in resting heart rate, a decrease of 1,600 daily step count and an increase of 35 min of night sleep were observed after a second mRNA vaccine dose[7]. Yet these findings tracked well with established knowledge of subjective assessments of reactogenicity, such as significantly greater changes in those receiving the Moderna versus the Pfizer/BioNTech vaccine and in those receiving the first dose response in people with prior COVID-19 infection (Fig. 1).

The potential value in identifying these small, individual changes was demonstrated by Mason et al.[9] in their study of over 1,000 individuals with wearable data from a smart ring and with post-vaccination SARS-CoV-2 receptor-binding domain antibody levels. They identified a significant and direct correlation between the change in several physiological parameters and immunogenicity, with the strongest independent predictor being temperature deviation. These finding are interesting considering prior work that has found that in some but not all studies, prophylactic antipyretic therapy can diminish the immunologic response to vaccine[10]. The ability to measure inflammation following vaccination has the potential, after being confirmed with rigorous prospective studies, of identifying individuals who may not develop an adequate immune response after vaccination.

Beyond the potential association between physiological changes and immunogenicity, objective evidence of the real-world behavioral impact of vaccines can aid in the design of safer, better-tolerated vaccines. The limitations of capturing this information using only subjective surveys is highlighted

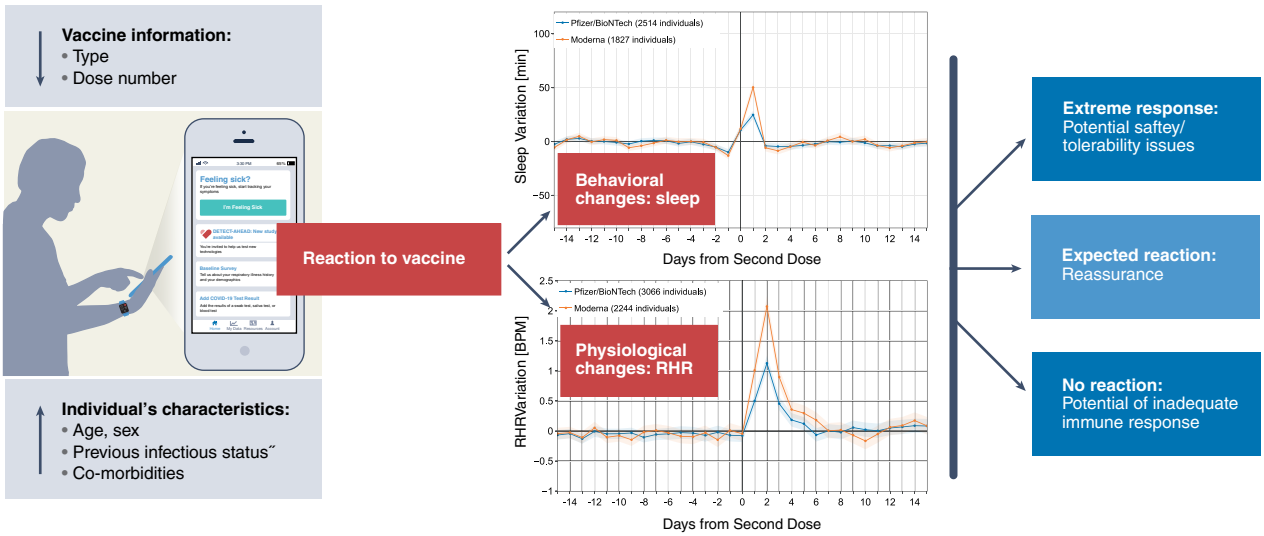

Fig. 1 | Physiological and behavioral changes post vaccination. Monitoring physiological (resting heart rate, RHR) and behavioral (sleep) changes post vaccination to identify vaccine response. Graphs reproduced with permission from ref. [7], Springer Nature.

in an analysis of reported adverse events in the placebo-controlled COVID-19 vaccine trials that found that >50% of the systemic adverse events reported could be attributed to a nocebo response[11]. Measurement of changes in activity type and duration, sleep quality and duration, sedentary time, posture and more, relative to a person's baseline before vaccination, can tell a more accurate and complete story of the severity of reactogenicity.

Although we find these early data encouraging, there still is a good deal to learn before wearables can become a standard part of vaccine development and treatment. For one, the current data are based on surprisingly sparse individual data — typically just one data point a day per parameter. Ongoing studies using medical grade wearable sensors with continuous high-fidelity data capture surrounding vaccination will help clarify the value of much deeper data (for example, ClinicalTrials.gov Identifier: NCT05237024). Most importantly, there is a need for more real-world data, with simultaneous testing of humoral and cellular immunogenicity, along with subjective symptoms. The ultra-rapid development of remarkably successful mRNA vaccines against COVID-19 foretells the future potential for this technology to address not only infectious diseases, but much more. Wearable technologies, passively and longitudinally tracking individuals without interfering with their day-to-day life, can help to realize the potential of individualized care based on a person's unique response to inflammatory stimuli. ❐

Giorgio Quer ✉, Eric J. Topol and Steven R. Steinhubl

Scripps Research Translational Institute, La Jolla, CA, USA.

✉*e-mail: gquer@scripps.edu*

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The BioInnovation Institute as a catalyst for European life science startup creation

To the Editor — Although a few European countries have had success in creating life science startups[1], the continent as a whole still lags behind the USA in terms of number of startup deals and of total investments[2]. To try and harness the untapped potential of European research, Denmark's Novo Nordisk Foundation (NNF) has established the BioInnovation Institute (BII). The institute's model relies on four pillars: first, knowledge within the BII team; second, access to a very large network of investors, industry experts and government experts; third, the availability of a company incubator with state-of-the-art laboratory facilities; and fourth, founder-friendly financing in the form of convertible loans to startups and of grants for academic company-creation projects. The combination of these four pillars not only supports accelerated translation of academic research into startups but also catapults these startups to financeable inflection points.

BII is an independent not-for-profit institute run by the BII Foundation. This foundation owns a commercial arm that runs the company incubator (operated by BH Holding) and also provides the funding for the convertible loans and for grants to academics. In 2018 it was established as a three-year initial operation within the NNF, with funding of roughly $60 million; for the period 2021 to 2030, BII is now a standalone institute that has been allocated an additional >$525 million in NNF funding.

The institute carries out activities under four central pillars (see Fig. 1). The ability to cover all these four pillars is due to generous funding from the NNF, which has also enabled BII to achieve a critical mass of operations. Scale is important for securing good applicants to our programs, for attracting high-quality staff and for building an extensive network. This scale of resourcing has also enabled BII to go beyond traditional therapeutics-oriented biotech and to support startups in other areas, such as healthtech and industrial biotech.

The first pillar, 'knowledge', is provided by staff with a deep understanding of science, engineering, business development and investments. The BII staff are actively engaged in scouting for relevant cases through outreach to universities and also employ an in-house software platform called EagleScout for scouting in specific scientific areas and geographic locations. When companies enter our programs, the BII staff work closely with the companies and assist in building the business case and team. This extensive support to the startups is costly, but it is critical for early-stage company formation.

The second pillar, 'network', connects participants with a wide range of experienced investors, scientists, clinicians, governmental organizations and industry collaborators. To enter BII's portfolio, companies must provide a clear strategy for how they can achieve financing, typically from venture capital funds, so they can move toward an exit in the long run (via a tradesale or floatation on a public stock market) with clear goals related to their scientific programs, to the business model and to team development. Once companies have been accepted, BII facilitates contacts with several business collaborators (for example, legal, intellectual property, accounting and contact research organizations) that can provide either pro-bono support or substantial discounts on market rates. The institute also facilitates contacts to the European life science industry, providing in-depth and up-to-date advice on regulatory affairs, reimbursement models, scale-up, clinical trial design, etc. Finally, BII has established a very large network of investors consisting of both European and US-based investors that engage in virtual pitches with the objective of providing feedback to our portfolio companies. To date, BII has facilitated >100 startup pitches to over 30 different investors.