IN brief

Million veterans sequenced

In what may prove to be the largest longitudinal study of its kind, the US Department of Veterans Affairs (VA) Million Veteran Program awarded in March its first contract to Personalis of Menlo Park, California, to

sequence and analyze the complete genomes of more than 1,000 veterans in the first phase of its multiyear Million Veteran Program (MVP). The sequence data will be added to an already wide variety of health, lifestyle and military-exposure information garnered from self-reporting and medical records that have been maintained in electronic form for at least 15 years. As of mid-May the program had enrolled more than 150,000 veterans and expects to enroll about a million veteran volunteers in total over the next five to seven years, with the VA currently expanding its biobank to accommodate the deluge of clinical samples. "Our goal is to continue to sequence as many MVP samples as our budget will allow, in addition to conducting other types of analyses," explains VA spokesperson Kendra Schaa. The combination of whole genome sequencing with very extensive electronic medical records will be a major step forward in terms of discovering the genetic and mechanistic bases for disease, says John West, CEO of Personalis, the company contracted to do the initial sequencing and genetic analysis. The genome sequencing and genome-scale genotyping—subcontracted by Personalis to San Diego-based Illumina—will query 100-base reads at a minimum of 30x coverage, generating about a billion reads per genome sample. Neither extensive longitudinal patient studies (such as the Framingham Heart Study) nor whole genome sequencing studies to catalog human variation (e.g., the 1000 Genomes Project) are new. Yet a wave of more recent longitudinal whole genome sequencing studies—including the UK10K Project—relies heavily on a highly standardized, electronically accessible, set of clinical data including a "relatively rich set of molecular phenotypes," with which to correlate deeper genetic findings mapped to an updated and corrected reference sequence, explains West. Genetic variants—especially the very rare ones—found in these studies to be associated with complex phenotypes may not lead to the immediate cause of a disease, let alone directly to its cure. But "every variant that points to a disease also points to a gene or a biological mechanism," says Nicole Soranzo of the Wellcome Trust Sanger Institute in Cambridge, UK, co-chair of the cohorts group of the UK10K project. MVP and UK10K (slated to be finished in September) are making their findings freely available to colleagues around the world. "I do expect that we will be mining this data for quite a long time to come," predicts Soranzo.

Josh P Roberts

and bladder cancers apparent in Forxiga's clinical trials are additional concerns that can only be ascertained with long-term, post-market usage. Diamant says, "We need to really watch bone health because diabetes is a chronic disease and people are going to be using these drugs for a number of years."

Invokana's long-term cardiovascular outcomes study—which FDA requires of all diabetes drugs—should provide some answers on the SGLT2 inhibitor's potential chronic side effects. John Buse, chief of the division of endocrinology at the University of North Carolina School of Medicine in Chapel Hill, who is an investigator on that trial, doesn't expect those data to be available until 2018. Data from Januvia's cardiovascular trial are expected this fall, and results from Bristol-Myers Squibb and AstraZeneca's Byetta (exenatide) later still, because glucagon-like peptide 1 (GLP-1) receptor agonists were not as widely adopted as the DPP-4 inhibitors.

These trials also should shed light on the two drug classes' potential for stepping up the risk of pancreatitis and pancreatic duct metaplasia (a type of pre-cancer), which were findings highlighted recently by a group of academic researchers examining a small number of pancreatic tissue samples from patients who had died from unspecified causes (*J. Am. Med. Assoc. Intern. Med.* 173, 534–539, 2013). FDA announced on March 14 that it intended to obtain and evaluate the samples and the researchers' methodology to further investigate these findings. Although the product labeling for DPP-4 inhibitors and GLP-1 receptor agonists already warn about the risk of acute pancreatitis, this was the agency's first communication about the potential risk of pancreatic pre-cancer. "My guess is these drugs don't cause pancreatic cancer, but there are data out there suggesting otherwise," notes Buse.

In Europe, Forxiga's initial uptake has been slowed by reimbursement issues, rather than safety concerns. Forxiga has been launched in the UK, Germany and Denmark, but "because of different reimbursement systems across Europe, many colleagues including myself can't prescribe it yet," says Diamant. In the UK, where the drug's price is £36.60 (\$56.20) per month excluding value-added tax, the drug did not receive the go-ahead from the UK National Institute for Health and Clinical Excellence (NICE). On February 1, NICE announced it was unable to recommend Forxiga in combination with other diabetes drugs because of concerns over the validity of meta-analysis data comparing Forxiga combinations against DPP-4 inhibitors, GLP-1 receptor agonists and

thiazolidinediones (TZDs). NICE requested additional evidence and said it will publish final guidance in June. The decision did not include Forxiga monotherapy. Although Invokana is priced slightly higher than the DPP-4 inhibitors, with a wholesale acquisition cost of \$263.10 per month compared with \$246 for Januvia, Butler notes that insurance co-pay amounts need to be taken into consideration when weighing a drug's potential uptake. "While the reimbursement remains to be seen, Johnson & Johnson [Janssen] is usually really good with that. They engage payors early," Butler comments.

The FDA rejected Forxiga in January 2012, likely due to the bladder and breast cancer concerns. Dominski says Bristol-Myers will provide the agency with additional data from ongoing studies, and expects to resubmit an application in mid-2013. Regulatory submissions for Forxiga were accepted for review in Japan in March and in China in January. Janssen's Invokana is under review at the European Medicines Agency (EMA)—both as monotherapy and fixed-dose combination with metformin—and the FDA is reviewing the combination, too.

Both Invokana and Forxiga have empagliflozin, an SGLT2 inhibitor from Boehringer Ingelheim of Ingelheim, Germany, and Eli Lilly of Indianapolis, on their heels. The companies submitted a new drug application (NDA) to FDA for empagliflozin on March 25, and EMA accepted a Marketing Authorization Application for review on March 26. On April 29, Merck also entered the SGLT2 inhibitor space with a partnership with New York-based Pfizer to develop and commercialize Pfizer's ertugliflozin and fixed-dose combinations of ertugliflozin with metformin and with Januvia. The monotherapy is expected to enter phase 3 testing later this year.

The diabetes space could be shaken up further with Lilly's dulaglutide, a once-weekly injectable GLP-1 receptor agonist that has met the primary endpoints in five phase-3 trials, including one trial in which it showed superior efficacy to once-weekly Bydureon (long-acting exenatide) from Bristol-Myers and AstraZeneca. Butler notes that dulaglutide has a smaller needle gauge compared with Bydureon, whose large needle gauge causes nodules at injection sites. Lilly plans to submit the compound to regulatory authorities in 2013. Merck's once-weekly oral DPP-4 antagonist MK-3102 also recently entered phase 3 testing, with an NDA not expected until at least 2015. "This whole area continues to evolve; it is pretty interesting," Butler says.

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These drugs will still work even in patients in advanced stages of diabetes.