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Short Takes

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Seeking a Million Patients to Deposit Genomes. Gina Kolata. NYT Tuesday, March 20, 2018, D1

Flash Summary: The goal of this biobank and database is to enroll one million patients who represent all ethnic and racial groups in the United States. People who enroll will have their genomes sequenced, provide medical records, and give routine blood samples to the database. Surveys about diet and health habits will be required and many will wear physiologic tracking devices. The program is called "All of Us." Dr. Francis Collins, the director of the NIH, feels this project will be transformative. The Congress has authorized over 1.455 billion dollars over 10 years for this study.

Bottom Line: According to the article, the program was started three years ago and no patients to date are enrolled. Some organizations initially contracted with the program have bowed out because of meetings and paperwork involved with compliance. Other organizations, including biotechnology companies, hospital systems, and the Department of Veterans Affairs, are doing similar albeit smaller biobank projects with overlapping goals.

Some pitfalls include: not enough sequencers available to sequence 1 million persons and the study requires genetic counselors to be available to inform enrollees about the potential for genetic diseases. These are real pitfalls. It is my experience that genetic counselors are very hard to come by even in a clinical setting. So how is the NIH going to counsel 1 million persons in very complex genetic matters that are not fully understood? We might get mass anxiety here.

I have been involved with the NIH and clinical trials for about 30 years. It is my impression that requirements for clinical trials as well as recommendations for study design are more and more ossified, making studies not only difficult to execute but also increasingly difficult to recruit subjects. This study might offer real information to people who enroll but it is unclear how the enrollees will be treated and counselled. A million people with full genomic sequencing is a formidable clinical task. The NIH is proposing to be the geneticist and counselor for this whole population. For such a study, it is difficult to do an accurate power determination for sample size.

We have already discussed big science. The Human Genome Project was unnecessary in the end since Celera, a private company, sequenced the genome at the same time the NIH did with no government funds expended. Here, there are huge financial outlays in a study that I am not sure the NIH is capable of executing. The real problem is that over a billion dollars will not go to basic research and individual clinical trials. Is this what has become of the NIH, a pusher of grand proposals without a real outcome measure? Big science is often not a good idea. It's too costly with only a hope for a good outcome. During a reverse site visit, I was told by a Principle Investigator that now is the time of big science and if we only gave him 10 million dollars he would solve the riddle of a disease. He was funded and solved nothing. As we all learned in grammar school, hope is the one evil that did not escape from Pandora's Box. Scientific studies, especially very expensive ones, should be done only with some outcome metric, not with hand waving and the hope of lots of data.

Autoimmune Encephalitis Epidemiology and Comparison to Infectious Encephalitis. Dubey D, Pittock SJ, Kelly CR, et al. Ann Neurol 2018:166-177

Flash Summary: The authors evaluated the incidence and prevalence of autoimmune encephalitis compared to infectious causes. This is a population-based comparative study of autoimmune versus infectious encephalitis. Autoimmune encephalitis was diagnosed by the 2016 criteria whereas infectious etiology was confirmed by the presence of a pathogen. Incidence and prevalence rates were calculated. The rates of autoimmune encephalitis in 2014 was similar to infectious etiologies. The rates of recurrence were higher for autoimmune encephalitis. The incidence of autoimmune etiology increased over the years related to an increase in auto-antibody cases. Antibodies with the highest prevalence included: myelin oligodendrocyte glycoprotein, glutamic acid decarboxylase, unclassified neural antibody, leucine-rich glioma-inactivated protein, collapsin response-mediator protein, N-methyl-D-aspartate receptor, antineuronal nuclear antibody, and glial fibrillary acidic protein. The authors conclude that the rate of autoimmune encephalitis is now similar to infectious encephalitis.

Editor's note: Short Takes offers a brief analysis by Steven G. Pavlakis of selected articles that may be of interest to child neurologists. Papers that strike the fancy of the analyst or the editors are selected for inclusion, but we welcome suggestions.

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Bottom line: The diagnostic criteria for autoimmune encephalitis and the initial criteria include the following: a subacute or rapidly progressive altered mental status or psychiatric symptom with focal central neurological signs, new seizures, cerebrospinal fluid pleocytosis, and abnormal MRI brain excluding other etiologies. Patients were further stratified and considered autoimmune if they were antibody positive, had acute disseminated encephalomyelitis (ADEM), Hashimoto's encephalitis, limbic encephalitis, and the like. Some patients were excluded if there was uncertainty.

This was a population study in Olmsted County, Minnesota, which is served by the Mayo Clinic and where clinicians had access to the Mayo Clinic Neuroimmunology Laboratory. As such, this comprehensive neuroimmunology evaluation may not be available to most hospitals. At least in this setting, the diagnosis of autoimmune encephalitis is increasing, likely because of better diagnostic criteria as well as more comprehensive neuroimmunological testing. The antibody abnormalities in children might have a different prevalence, but the old adage applies here. If one looks carefully, one finds autoimmune encephalitis at rates not previously recognized and this is likely true of children as well. In fact it is my impression that children are more likely to have autoimmune encephalitis than infectious etiologies currently.

Bjùrk M, Riedel B, Spigset O et al. Association of folic acid supplementation during pregnancy with the risk of autistic traits in children exposed to antiepileptic drugs in utero. JAMA Neurol 2017, Epub 2017 Dec 26 2018;75: 160-168

Flash Summary: The study was performed in Norway on a mother and child cohort. The analysis was prospective an included 385 children whose mothers had epilepsy on antiepileptic drugs (AEDs) and a control group of 104,222 children whose mothers did not have epilepsy. Folic acid levels and AED levels were taken at 17 and 19 weeks gestation and from the umbilical cord at birth. Autistic traits were measured at 18 and 36 months using a check list and a questionnaire. Peri-conceptual folic acid use was determined by questionnaire.

The analysis showed that offspring had a higher risk of autistic traits if born of women who did not take folic acid while taking AEDs compared to mothers on AEDs with folic acid supplementation. The severity of the autistic traits was inversely associated with maternal plasma folate concentrations ($\beta = -0.3$; $P = .03$) and folic acid doses ($\beta = -0.5$; $P < .001$). Concentrations of AEDs were not associated with the extent of autistic traits.

Bottom Line: Of course, the study has limitations. Even though there was a control for socioeconomic status, other unmeasured confounders could exist between the folic acid supplementation group and those who did not take folic acid. In addition, apparently Norway does not supplement food with folic acid as is done in the United States. The strongest indicator that folic acid levels and autistic traits are associated comes from the inverse association of folic acid concentrations and autistic traits. It is known that at least some AEDs decrease folic acid concentration and it has been long known that folic acid supplementation decreases risk of birth defects. Finally, we do not know about the incidence of autism at age five years, so we only have data about traits at age 36 months. Here we have more data about the use of folic acid supplements in mothers with epilepsy on AEDs.

When I first saw this paper reviewed in *Neurology Today,* I had a different question. I accept that there is a link between low maternal folate and birth defects and also brain development. What is the link between maternal folic acid and autism? On a review of the literature, the data are all over the place. There is much written on the internet and in open access journals. Actually, high folic acid concentrations have been speculated to be associated with autism, as well as low. The important questions: are whether folic acid is necessary for brain development and whether it is protective for the development of autism. If it is, why? This is a question that might lead to some answers regarding the development of autism.