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BREAKING NEWS
HAZARDS TO HEALTH ON THE FDA FAST TRACK TO ACCELERATED DRUG APPROVAL

As reported in the July-August issue of IHN, on June 7 the US FDA gave fast-track approval for an Alzheimer's disease drug despite opposition by 10 of the 11 members of their Advisory Committee with 3 promptly resigning. This approval requires follow-up studies which in the case of the Alzheimer's drug, the company was given a remarkable 9 years to perform. The rationale for such requirement is to ensure that all drugs granted accelerated approval indeed offer actual clinical benefit. This event has prompted a number of commentaries in medical journals, most expressing disapproval, concern, and disbelief.

A study that just appeared in the *BMJ* (*British Medical Journal*) which investigated the post-fast track approval history of 10 cancer drugs that were granted approval but failed to improve the primary endpoint in post-approval trials.[1] The trials presented for drug approval were based on surrogate endpoints. Cancer related surrogate endpoints generally measure changes in tumor size, or time to progression of the cancer. While these measures may ultimately be shown to predict meaningful clinical benefit, the authors point out that this is often not the case. The most common clinical endpoint is overall survival time.

The study investigated 10 drugs targeting 18 indications for cancer drugs that received accelerated approval but subsequently failed to show improvement in primary clinical efficacy in the confirmatory trials. Post-approval events tabulated were voluntary withdrawal, conversion to regular approval, revoked approval, and negative results from confirmatory trials, and reapproval for a different dose or patient population. It was observed that even when the indication was withdrawn, the withdrawal was sometimes delayed for several years after initial approval and the indications continued to appear in guidelines. The authors also noted that the positive post-approval trial requirement has sometimes been waived even though the required trial failed to meet the primary endpoints.

As of July 2021, of the 18 accelerated approval indications with negative post-approval trials, 11 were voluntarily withdrawn, 1 revoked by the FDA, and 6 remain, 2 via conversion to regular approval status and 4 continue with accelerated approval status despite their failed approval trials. The authors point out that this reflects the lack of

fulfillment of the compromise between speed and evidence that justifies the accelerated approval pathway.

Another example was presented in a letter to the *JAMA Oncology* journal (published online Sep 23, 2021) which found for the bladder cancer drug Atezolizumab that in the period after the drug was withdrawn because of no demonstrated clinical benefits, for 2018-2019 there were 6200 paid claims representing $46 million in Medicare spending for this drug.

VITAMIN D AND CANCER INCIDENCE AND MORTALITY

In a just reported study of 8700 individuals with 25-hydroxyvitamin D data and no history of cancer, endpoints in the follow up were cancer incidence and mortality. The median follow-up was 4.6 years.[2]

It was found that compared to participants with 25(OH) D values of 20 to 50 ng/mL (normal), those with values less than 12 ng/mL had a greater incidence of nonskin cancer after adjustment for confounding. In addition, compared to the reference group, those with 25(OH) D values <12 ng/mL and 12 to 19 ng/mL experienced an increase in cancer-related mortality.

ANOTHER CUP OF COFFEE PLEASE. HOLD THE ARRHYTHMIA

The dogma that caffeine increases the risk of cardiac arrhythmias is well established. However, this view is poorly substantiated. A recent study published in *JAMA Internal Medicine* appears to contradict this view.[3] Over 386,000 individuals of mean age 52 and about half female were followed for 4.5 years with about 7000 developing incident arrhythmias. Each additional cup of habitual coffee was associated with a 3% decrease in the incidence of atrial fibrillation and/or flutter, or supraventricular tachycardia. The influence of either caffeine metabolism or genetic effects was ruled out. In fact, this appears to be the first study to use genetic analysis to address the caffeine metabolism issue. An editorialist points out that the study sample was limited to patients with no formal prior diagnosis of arrhythmia and thus it remains unclear if coffee consumption could aggravate existing cardiac arrhythmias disorders.[4]

ALCOHOL AND INCIDENCE OF TYPE 2 DIABETES

This is part of an ongoing series of IHN pieces concerning alcohol consumption and health risks/benefits. It seems that the common feature of the existing studies is that low to moderate consumption can be protective for primary prevention of various diseases and reduces risk to less than found for abstainers. Type 2 diabetes is no exception and there have been an amazing number of studies. On PubMed, the title words *alcohol* and

diabetes bring up 428 citations, carbohydrates and diabetes 123 and diet and diabetes 2500 as of September 10.

Studies showing this protective effect go back to around 2000. Between 2005 and 2020 there have been 6 meta-analysis studies or systematic reviews published concerning alcohol and diabetes.

- A meta-analysis[5] of epidemiological follow-up studies published in 2005 found that moderate alcohol intake was protective with a relative risk of 0.72. A value of > 1.0 represents the threshold for positive risk. Moderate intake was defined as about 5-30 g/d of alcohol (30 g/d being two large drinks per day). The reduced risk was seen in men as well as women.
- A 2009 meta-analysis of 20 cohort follow-up studies which used for comparison lifetime abstainers found a U shaped dose relationship with the greatest protection for incident type 2 diabetes at 22 g/d for men and 24 g/d for women.[6] Risk became positive at 60 g/d for men and for women at 50 (point where the risk ratio exceeded 1.0).
- A 2016 meta-analysis involving 26 studies with over 700,000 individuals (M/F ratio 0.64) found a U-shaped dependence on alcohol intake.[7] Light, moderate and heavy intake was defined as 0-12, 12-24 and ≥ 24 g/d respectively. Comparison was made with minimal intake. For men the largest protection was found at around 20-25 g/d and for women 25-25 g/d. Even at around 60 g/d, protection was still seen for both men and women.
- A 2015 meta-analysis involving 1.9 million individuals from 38 prospective follow-up studies found no protective effect over a wide range of intakes. However, when the results were stratified for Asian and non-Asians a protective effect was seen only for the latter which was somewhat smaller than that found in the studies described above.[8] This was consistent with a meta-analysis in 2020 of just Asian men where no protection was seen overall and the weak U-shaped dose response became non-significant at around 10-15 g/d.[9]
- A review published in 2017 examined the occurrence of the light-moderate intake protection for diabetes in 16 studies and found that all 16 studies observed this result. All the studies had at least 10,000 subjects with subjects from a variety of countries.[10] The largest studies were based on data from the Health Professional's' Follow-Up Study, The Physicians' Heath Study, and the Nurses' Health Study, all high-profile prospective follow-up studies.
- A recent meta-analysis of 16 studies examined the dependence of the protective effect of alcohol on the type of drink.[11] Wine was the big winner (risk ratio 0.85, statistically significant) whereas beer and spirits failed to yield significant results. Dose response found that only wine maintained statistically significant response up to 60 g/day. Beer failed at around 20 g/day and for sprits there was no protection (relative risk > 1.0).

- Wine consumption throughout life was found to be inversely associated with type 2 diabetes risk for French females, mean age 53 years, but only for overweight individuals (BMI ≥ 25 kg/m^2). A strong dose dependence was found vs. abstainers over the range < 0.5 drinks per day to ≥ 2 drinks/day.[12]
- A cohort study from Denmark with 77,000 participants and a median follow-up of 5 years found significant protection up to 32 g/day intake for men and 28 g/d for women.[13] At these limits the protection was still large. The maximum protection was found at 15 g/day for men and 10 g/day for women with women having greater protection, achieving a hazard ratio of 0.4.

In the studies we have been discussing, the risk curves showing protection according to dose are smooth and such that from the minimum there is a slow change where one glass either way makes little difference which emphasizes that this is a rather crude measure.

POSSIBLE EXPLANATIONS FOR THE PROTECTIVE EFFECT

The most comprehensive analysis appears to be the one reported by Shrieks *et al.*[14] They conducted a meta-analysis of studies of alcohol and glycemic endpoints. It was concluded that moderate alcohol consumption did not influence estimates of insulin sensitivity or fasting blood glucose levels but decreased fasting insulin concentrations and HbA1c. However, it was found that moderate alcohol consumption may improve insulin sensitivity and decrease fasting insulin concentrations in women. There was no dosage or consumption duration effect seen in the results. The observation that alcohol may decrease HbA1c suggests alcohol suppressing the acute rise in blood glucose after a meal which would decrease glucose concentrations over time and lower this measure of long-term average levels.

The prominence of wine as being associated with protection suggests the need for studies designed to explain this observation. However, larger studies with alcohol-free wine appear to be unrealistic.

ALCOHOL CONSUMPTION ALONG WITH DIABETES

The official position appears to be that moderate drinking is not considered harmful. However, note that alcohol consumption along with diabetic medications can cause hypoglycemia, especially on an empty stomach. The issue of whether or not alcohol calories count is debatable but what appears to be the definitive study suggests the answer is no, and in fact substituting alcohol calories for carbohydrate calories (50% of calories) in a metabolic ward setting produced a significant weight loss.[15]

FINAL REMARKS

There is the ever-present problem of underestimation. What is being defined as low to moderate may be in real life be more alcohol per day than what is being assumed. While estimates of underestimation range from a factor of 2 to 5, in fact in any given study one has no idea how serious the problem might be. However, it seems safe to assume that advice to limit intake to 2-3 drinks per day may be based on data where the

intake was actually 3-4 or even 4-5. This should provide comfort to those who find the guideline recommendations a bit too restrictive.

On the other hand, intake guidelines should take into account all health benefits and risks in order to make a really informed decision. Evidence of benefits for disease prevention include immune function, cardiovascular disease (see September IHN), cancer, type 2 diabetes as discussed, metabolic syndrome, and neurologic, pulmonary, and gastrointestinal diseases.

https://www.ajevonline.org/content/62/4/471.short

Risks include liver diseases associated with high intake and esophageal cancer risk which is a complex issue having a strong genetic component but otherwise apparently not a serious problem, as will be discussed when alcohol and cancer is reviewed. There is risk of drug interactions but generally prescriptions come with a warning. Women at risk of becoming pregnant and individuals with the heart rhythm disorder ***atrial fibrillation*** should totally avoid alcohol. Recognized non-health risks include accidents, addiction, antisocial or dangerous behavior, and family and employment problems. However, it seems important to consider that human alcohol consumption goes back many centuries and humans appear successful in identifying dangerous food and drink and passing along information from generation to generation. After all, moderate wine consumption is widespread. It is a notable characteristic of the Mediterranean diet.

The question naturally arises. Why does alcohol appear to be a universal health food if consumed with moderation? The multiplicity of diseases implicated renders the answer very important.

EDITING HUMANITY
THE GENOME EDITING REVOLUTION THAT MAY FOREVER CHANGE MEDICINE

Imagine a couple siting in the elegant office of a specialist in providing custom designed children. There are many issues and decisions to be made. They more or less fall into two categories, disease issues and other issues. The disease issues involve possible genetic disease risk factors from the parents, either one or both. There are both rare diseases and more common ones driven partly or mostly by genetics. A classic example is sickle cell anemia which can now be cured. The specialist simply indicates that a list can be prepared after genome sequencing and the couple must make a choice of priorities. The second set of issues involves such characteristics and height and body build, and eye and hair color. However, this list also contains much more serious issues such as IQ. Once the embryo is created by artificial fertilization, the path to test tube babies, and has developed for several days, its genome can be edited to customize it. Changes may be passed to future generations, something critics find highly alarming. Finally, the embryo is implanted.

THE CRISPR TWIN BABIES

This has already happened. At this writing there are only three known custom babies in the world. No one knows if there are more simply carefully concealed. The twin babies born in China were designed by He Jiankui, then associate professor at Southern University of Science and Technology in Shenzhen. They were designed to be resistant to HIV, a serious problem involving severe discrimination even though the prevalence is low in the area where the parents lived. Because the editing technique uses a laboratory tool known as CRISPR (clustered interspaced short palindromic repeats), they are commonly called the CRISPR babies. CRISPR also describes microbiological constructs that bacteria have used for millions or even billions of years to defend themselves from viral invaders. Knowledge of how this worked inspired the development of the laboratory version by Jennifer Doudna and Emmanuelle Charpentier, recipients of the 2020 Nobel Prize in Chemistry for this work. The gene editing by He Jiankui was done *in vitro* followed by implantation. Since the CRISPR babies were born, Cinna has released no updates. He Jiankui was also responsible for one other baby, but the details are suppressed.

Jiankui is now in jail and has a lifelong prohibition doing research in reproductive biology. He was convicted of intentionally dodging supervision and raising funds on his own to carry out gene editing intended for reproduction, which was explicitly banned by Chinese regulators, as well as faking and using the required ethical review certificate. Two of his colleagues were also convicted.

The CRISPR twins were born in November 2018 and will be 3 years old soon. Despite the scientific importance of this event no information has been released on subsequent testing to determine the current genetic status of the twins nor if there is evidence of adverse effects. An unpublished paper buy Jiankui circulated among interested scientists revealed only partial success in the editing and there were some off target edits. This deprives the world genome editing community of unique information.

The explosion of interest in gene editing with the advent of the CRISPR technology is illustrated by 10,000 citations with CRISPR in the title on PubMed as of September 30, 2021, but only 7 clinical trials. The phrase *genome editing* yields 2900 citations and no clinical trials. Several gene modification methods were in use before CRISPR. They have been successfully applied to curing rare genetic diseases by removing or disabling the genetic blueprint. They are being replaced by CRISPR technology.

Gene editing to modify or cure the following diseases is currently ongoing for cancer, blood disorders, cystic fibrosis, Duchenne's muscular dystrophy, and Leber congenital amaurosis which is the most common cause of inherited childhood blindness. AIDS—cure or protection against, and COVID-19 for screening tests and attacking the virus. However, more are under consideration or therapy development.

REGULATORY OBSTACLES AND COST

The current challenge is how to regulate gene editing to ensure safety while also keeping costs from becoming astronomical. These are uncharted waters. In addition,

new CRISPR technology is being introduced frequently. The development of a new CRISPR called CASPRCasMINI has just been published which may be a real therapeutic breakthrough.[16] The need for personalization for many gene disorders requires an editing tool which may be expensive to design. It does not appear practical that each new unique therapy requires regulatory approved, especially if the traditional requirements are enforced, and to enforce them would be disastrous to the whole endeavor and used to justify astronomical prices for treatment. The ethical issue of germ line editing, e.g., sperm, eggs or embryos, is challenging and controversial. The worldwide market is huge.

A demand for designer babies is inevitable including an expected response to preimplantation genetic testing. An example of a more serious issue is that each year there are approximately 250,000 babies born with sickle cell anemia. The worldwide need to cure genetic diseases is huge. The costs and availability for therapies for the diseases listed above and the many others being considered or already subjects of research cannot at this point be predicted. After all, the current genome revolution is probably the biggest health event to ever occur in the history of mankind.

CONCLUSION

Genome editing has experienced an explosion of research and development just in the past several years. The knowledge and skill possessed by these scientists and the financial support being provided to start-up companies, especially by venture capitalists, almost assures that many revolutionary and safe new therapeutic approaches are not more than a few years in the future.[17,18] Resolving the ethical issues associated with inheritable genetic modifications is also necessary but the overall therapeutic benefits rapidly developing are independent of this because disease issues can be approached without germline editing.

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These books provide an introduction to genome editing and all the major players in the sensational advances in genetics that have occurred in the past decade which fulfill may of the dreams prompted by the discovery of the double helix in 1953 by Watson and Crick. These books describe the revolution that is happening, the significance, the challenges the risks and the huge potential for improved human health and increased effectiveness of medical therapies.

- ***The Codebreaker. Jennifer Doudna, Gene Editing and the Future of the Human Race.*** **2021.** Walter Isaacson. The story of the career of Jennifer Doudna, a biochemist and professor in the Department of Molecular and Cell Biology at the University of California Berkley, and her contributions to the science of gene editing which is dramatically changing the application of genetics in medicine are impressive. Along with a colleague Emmanuelle Charpentier she was awarded the Nobel Prize in Chemistry in 2020 for the discovery of the gene editing protocol called CRISPR.
- ***The Crack in Creation. Gene Editing and the Unthinkable Power to Control Evolution.*** **2018.** Jennifer Doudna and Samuel Sternberg. Jennifer Doudna's own account of her experiences as a Professor of Biochemistry at the University

of California, Berkeley and a being a major player in the discovery and development of CRISPR gene editing. Provides a good discussion of the ethical issues and the heavy responsibility that comes with the power to rewrite the code of life.

- ***Editing Humanity. The CRISPR Revolution and the New Era of Genome Editing.* 2020.** Kevin Davies. The author has a PhD in molecular genetics from the University of London and has written several books describing the genetic revolution along with coauthoring the new edition of *DNA: The Story of the Genetic Revolution* by James Watson and Andrew Berry. He provides a somewhat different view of the power and potential of CRISPR, especially the ethical issues including altering genes where the changes can be passed on to future generations.
- ***The Genome Odyssey. Medical Mysteries and the Incredible Quest to Solve Them.* 2021**. Euan A. Ashley, MD, PhD, Professor of medicine and genetics at Stanford University. The author shares fascinating stories of real-life patients facing rare and devastating diseases and how breakthroughs made possible by decoding their genetic makeup guided the path to a genetic therapy and a cure. Described as a landmark narrative by a scientist who had a front-row seat in this journey by virtue of his own scientific work.
- ***CRISPR People. The Science and Ethics of Editing Humans.* 2021.** Henry T. Greely. The author is Professor of Law, Professor by Courtesy of Genetics and Director of the Stanford Center for Law and Biosciences at Stanford University. The book provides a comprehensive history of the CRISPR twins and the ethical issues, implications, and ramifications of this historic event as well as much interesting information about genome editing and germline editing, and the origin of CRISPR.

BEWARE OF A 10-YEAR HEART DISEASE RISK WHICH MAY BE GROSSLY OVERESTIMATED

After a periodic checkup and blood work, it appears to be common practice for the 10-year risk of heart attack or stroke or heart disease in general to be estimated with an online calculator. In 2015 readers were warned that there was evidence and concern that the latest calculator (AHA/ACC pooled equations calculator) seriously over-estimated risk with the result that many were over the threshold for guideline recommended statin therapy. In fact, a paper published in 2015 compared 5 risk calculators with the predictions made from the modern database developed in connection with the Multiethnic Study of Atherosclerosis (MESA).[19] The overestimation for 4 calculators vs. MESA predictions was very large. In this comparison the two Framingham, the Adult Treatment Panel III and the AHA/ACC calculators had overestimates ranging from 25% to 115%.[19] these calculators are not based on recent data whereas the MESA calculator is.

Also in 2015 a detailed account was published concerning an online calculator based on the MESA database, the details of the algorithm, and the validation against two modern heart studies, the Heinz Nixdorf Recall Study (Germany), and the Dallas Heart Study (US).[20] The calculator gives the probability of a coronary heart disease (CHD) events over 10 years. The events are myocardial infarction (MI, heart attack), resuscitated cardiac arrest, fatal CHD, and revascularization only if individual also had prior verified angina. CHD deaths had to occur within 28 days after the MI. These are termed *hard* events and the goal is to avoid so-called soft events or subjective endpoints which inflate the calculated risk. For example, endpoints for other calculators also include stroke, angina, peripheral vascular disease, transient ischemic attack, and heart failure.

The overestimation problem is illustrated in the table below which examines the dependence on age and total cholesterol (TC) for the MESA databased calculator and the AHA/ACC most recent version online calculator. The calculator results are the 10-year CHD event probabilities without input of a coronary calcium score, expressed as percent risks for both men and women. The hypothetical individual has a total cholesterol of 150 mg/dL, HDL-C of 50 mg/dL, and a systolic blood pressure of 120 mmHg, and “no” as answer for all the questions such as medication use and family history. Note the strong age dependence with only a five-year age change. Note also that the MESA calculator finds only one risk > 7.5 %, the now standard threshold for advising cholesterol lowering, but the AHA/ACC calculator waves many red flags and the website comments on the results in terms of statin needs.

AGE	TC, mg/L	MESA, M	MESA, F	AHA/ACC, M	AHA/ACC, F
60	200	3.9%	1.9%	7.7%	3.1%
	250	5.1%	2.4%	9.5%	3.7%
	300	6.5%	3.1%	11.1%	4.3%
65	200	4.9%	2.3%	11.5%	5.1%
	250	6.3%	3.0%	12.1%	5.8%
	300	8.1%	3.9%	15.1%	6.3%

The benefit of incorporating the calcium score into the MESA calculator algorithm may seem to some intuitively obvious. However, many have never had a coronary calcium CT scan and cannot take advantage of this feature. Mass screening with a CT scan appears unrealistic. However, since it is common to have a score of zero, especially for those 50 or younger and certainly for women, also doing the calculation by putting in this score will indicate the personal impact of this stage of atherosclerosis. There is also an online MESA Calcium Calculator which uses age, gender, and race and lists four percentiles for prevalence of coronary plaque burden quantified by the Coronary Artery Calcium Score (CACS). In the table below, results by age for men and women of white race are given. The CACSs cover a wide range from zero to quite high with significant gender and age dependence. This provides a rational for a strong age dependence of risk for above age 60 and for the striking gender dependence in general. This table will allow selecting a CACS input for the MESA risk calculator according to a selected percentile, for example middle of the road at 50$^{th.}$ percentile. The table also shows the prevalence of a zero CACS. When the CACS is not entered, the creators of the MESA

calculator presumably have a way of estimating an average value, but it is not disclosed. Rough exploratory calculations suggest it is close to the 50th percentile.

MESA Calcium Calculator

MEN				
AGE	25th	50th	75th	90th
50	0	0	22	110
60	0	28	155	452
70	21	145	540	1345
80	103	385	1200	2933

WOMEN				
AGE	25th	50th	75th	90th
50	0	0	0	0
60	0	0	16	102
70	0	13	119	390
80	20	106	370	921

The AHA/ACC calculator is probably vastly more recognized and popular than the MESA with the latter probably unknown to many physicians. If one tries other calculators such as QRISK, Framingham, or Mayo Clinic, similar very high risks will be found.

Some may wonder why the calculator has a question regarding hypertension medication. It is not because these medications pose an intrinsic risk, but rather those treated for hypertension tend to be a higher risk population. The answer to the question captures a combination of the increased risk and the beneficial effect of the medication. The same applies the lipid-lowering question.

The bottom line seems to be, only allow 10-year risks from the MESA calculator to influence the evaluation of heart disease risk. *Mesa heart risk calculator* will bring up the website with Google. A copy of the blood work is needed. The calculator automatically does unit conversions for cholesterol. Once one has a presumably reliable 10-year event risk, comparison can be made with the now official 7.5% and the traditional 10% thresholds for blood lipid lowering intervention.

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