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Emerging Trends in Clinical Research: With Implications for Population Health and Health Policy

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Policy Points:

- Significant advances in clinical medicine that have broader societal relevance may be less accessible to population health researchers and policymakers because of increased specialization within fields.
- We describe important recent clinical advances and discuss their broader societal impact. These advances include more expansive strategies for disease prevention, the rise of precision medicine, applications of human microbiome research, and new and highly successful treatments for hepatitis C infection.
- These recent developments in clinical research raise important issues surrounding health care costs and equitable resource allocation that necessitate an ongoing dialogue among the fields of clinical medicine, population health, and health policy.

Context: Developments in clinical medicine have important implications for population health, and there is a need for interdisciplinary engagement among clinical medicine, the social sciences, and public health research. The aim of this article is to help bridge the divide between these fields by exploring major recent advances in clinical medicine that have important implications for population health.

Methods: We reviewed the most cited articles published from 2010 to 2015 in 5 high-impact clinical journals and selected 5 randomized controlled trials

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and 2 related clinical practice guidelines that are broadly relevant to population health and policy.

Findings: We discuss the following themes: (1) expanding indications for drug therapy and the inherent medicalization of the population as highlighted by studies and clinical guidelines supporting lower blood pressure targets or widespread statin use; (2) the tension in nutritional research between quantifying the impact of isolated nutrients and studying specific foods and dietary patterns, for example, the role of the Mediterranean diet in the primary prevention of cardiovascular disease; (3) the issue of high medication costs and the challenge of providing equitable access raised by the development of new and effective treatments for hepatitis C infection; (4) emerging clinical applications of research on the human microbiome as illustrated by fecal transplant to treat *Clostridium difficile* infections; and (5) the promise and limitations of precision medicine as demonstrated by the rise of novel targeted therapies in oncology.

Conclusions: These developments in clinical science hold promise for improving individual and population health and raise important questions about resource allocation, the role of prevention, and health disparities.

Keywords: clinical trials, social sciences, public health, health equity, drug costs.

DEVELOPMENTS IN CLINICAL MEDICINE HAVE IMPORTANT implications for population health, health disparities, and the setting of societal priorities for resource allocation. There is, therefore, a need for engagement among researchers and practitioners in clinical medicine, the social sciences, and population health. However, because of the increasing subspecialization within medicine, clinical advances may be less accessible to audiences in other fields. This divide between disciplines can lead to considerable delays in implementing clinical science to improve the health of populations.[1] For example, studies in the United States and Europe have demonstrated an incomplete and variable uptake of interventions supported by high-quality research, including population health initiatives such as screening and preventive care.[2-4] In addition to uptake, a broader public health and policy audience should discuss developments in clinical medicine that would be resource intensive to apply or that may divert from other priorities such as social equity.

The aim of this article is to help bridge the divide between clinical medicine and nonclinical fields that study population health, by

exploring major recent advances in clinical science that have important implications for population health. In the clinical literature, because randomized controlled trials (RCTs) are pivotal in changing clinical practice, we focus on the most frequently cited clinical trials published in major medical journals from 2010 to 2015. We discuss trials that hold a broad significance for population health and policymaking, situating these recent advances in biomedical research in broader social and economic contexts.

Methods

To identify articles and themes in the clinical literature to include in our article, we employed mixed methods, combining a literature search based on frequency of citation (as a proxy for impact in the clinical sciences), followed by purposive sampling based on interdisciplinary perspectives on which clinical developments were clinically novel and also were important to population health and health policy. We searched the Institute for Scientific Information Web of Science® database (Philadelphia, PA) on February 6, 2018, for the most frequently cited articles published from January 1, 2010, to December 31, 2015, in 5 of the highest-impact journals in clinical medicine (*New England Journal of Medicine, Journal of the American Medical Association, The BMJ, The Lancet,* and *Annals of Internal Medicine*). We did not extend our search beyond the end of 2015 to allow articles published at the end of the search period sufficient time to be cited. We selected the 300 most frequently cited articles based on Web of Science® citations and narrowed our focus to RCTs, based on the consensus of the clinical community that randomized trials have the greatest impact on clinical practice.[5] The selection of 5 RCTs for broader exploration involved purposive sampling based on our discussion as experts in population health (Subramanian) and in health services and policy (Laupacis), individuals at the intersection of these 2 areas (Chin-Yee, Verma, Razak), and practicing clinicians (Chin-Yee, Verma, Laupacis, Razak). This discussion incorporated the authors' opinions and perspectives and was based on (1) novelty and impact on clinical practice and (2) relevance to population health and policy. Identifying these important themes was an inherently subjective process and is not meant to suggest that these are the only or necessarily the most significant themes. Instead, our purpose was to review important

advances in clinical research for nonclinicians, and this approach reflects our best efforts to do so after a thorough review of high-impact studies.

Results

We selected 5 emerging themes: (1) Evidence supporting lower blood pressure targets is leading to expanding indications for drug therapy and medicalization of the population.[6,7] We examined this research in conjunction with a thematically related set of clinical guidelines regarding cholesterol and blood pressure.[7,8] (2) Nutritional research studying specific foods and whole dietary patterns, for example, the role of the Mediterranean diet in preventing cardiovascular disease,[9] is shifting away from its previous focus on quantifying the impact of isolated nutrients such as saturated fats and cholesterol. (3) The development of new and effective treatments for hepatitis C infection represents a major breakthrough but also raises challenges related to high medication costs and equitable access.[10] (4) Research on the human microbiome is finding important clinical applications, as illustrated by the use of fecal transplant to treat *Clostridium difficile* infections.[11] (5) Lastly, the rise of targeted therapies in oncology highlights the promises and limitations of precision medicine.[12] The articles we selected and the themes we discussed present clinical research at various stages: (1) research that is already being applied at a population level, (2) interventions that are ready for implementation but with ongoing barriers to populationwide application, and (3) new research paradigms that are in an early phase but could have a significant impact on population health.

Expanding Indications for Drug Therapy: The Medicalization of Prevention

SPRINT Trial and New Cholesterol-Lowering Guidelines

The past decade has seen a move toward a more aggressive control of risk factors for cardiovascular disease, with an expanding definition of what constitutes risk, which has led to a greater proportion of the population

now being considered eligible for drug therapy. High blood pressure and cholesterol are important risk factors for cardiovascular disease, and new research and guidelines support expanded eligibility for treating both.

The 2013 guidelines issued by the American College of Cardiology and American Heart Association (ACC/AHA) for the treatment of cholesterol to prevent cardiovascular disease, and the recommendations of the 2016 US Preventive Services Task Force significantly expanded the number of patients eligible for drug treatment based on evidence from RCTs.[7,13] Implementation of the ACC/AHA guidelines would increase the percentage of American adults eligible for statin therapy from 37.5% to 48.6%.[14] This represents an increase of 12.8 million in the number of statin users, with the majority (10.4 million) being individuals receiving statin therapy for primary prevention of cardiovascular disease.

Along with broadening the use of statin therapy, emerging clinical research supports lower treatment targets for blood pressure, with the ACC/AHA's 2017 guidelines greatly expanding the number of individuals who would be treated.[8] Prior to these guidelines, clinicians targeted a blood pressure of 140/90 mm Hg,[15] and it remained uncertain whether the more intensive blood pressure control would prevent death or adverse cardiovascular outcomes. The 2015 Systolic Blood Pressure Intervention Trial (SPRINT) investigated whether more intensive blood pressure control—aiming for a systolic blood pressure of less than 120 mm Hg—improved cardiovascular outcomes and survival. SPRINT demonstrated a significant reduction in major adverse cardiovascular outcomes and mortality in the intensive-treatment group, such that the number of individuals with intensive blood pressure control needed to treat to prevent 1 cardiovascular event was 61, and 90 to prevent death from any cause.[6,16]

Patients in the intensive-treatment group had a greater incidence of adverse events such as hypotension, syncope, electrolyte abnormalities, and acute kidney injury. The study faced several criticisms, including concerns about SPRINT's automated blood pressure measurement techniques, which are difficult to compare with those used in earlier studies.[17] SPRINT's external validity and applicability to real-world populations also were questioned, given that the trial excluded individuals living in nursing homes or assisted-living facilities, as well as individuals with dementia.

Despite these limitations, SPRINT's findings have greatly influenced subsequent Canadian[18] and American hypertension guidelines,[8] resulting in a redefinition of high blood pressure and a marked increase in the number of people eligible for treatment. Application of the 2017 ACC/AHA guidelines for managing high blood pressure increases the prevalence of hypertension from 31.9% to 45.6% in US adults, with antihypertensive medications being recommended for 36.2% of the adult population.[19] The expanding indications for statin use and blood pressure control in the recent guidelines continue to narrow the distinction between clinical and public health approaches to risk factor management.[20]

Risk Factor Medicalization Versus Rose's "Population Strategy"

With the goal of prevention, both the SPRINT trial and the new cholesterol and blood pressure guidelines have medicalized many individuals and have recommended lowering risk factors through drug therapy rather than societal changes and behavioral modification. This approach contrasts with conventional public health approaches to chronic disease prevention, with Geoffrey Rose's framework of a "population strategy" perhaps being the most influential.[21] The ultimate goal of Rose's population strategy is to shift the distribution of a population's risk factors through primarily nonmedical means.

Rose's population strategy for prevention was "radical" in the sense that it required broad societal change, but he noted that it was potentially the most beneficial and equitable means of improving population health.[22] At the time that Rose developed his theories, the population strategy stood in clear contrast to the "high-risk strategy," which, as the name implies, targets preventive actions to the highest-risk individuals.[20,22] The high-risk strategy was classically thought of as the domain of clinical medicine, in which physicians use medications to address patients' risk factors. Clearly, these prevention strategies are not mutually exclusive, and Rose argued that they ideally should be applied together to shift both the risk distribution and risk factor modification for high-risk individuals.[23] However, he saw the high-risk strategy as more "palliative and temporary," an approach to be used until the population strategy was effective.[24]

Rose's preference for mass solutions and structural changes rather than pharmacotherapy was influenced by the risk-benefit profile of the medications available at the time, particularly research demonstrating the adverse effects of the cholesterol-lowering drug clofibrate.[20,22] Clofibrate was one of the first cholesterol medications considered for mass prevention, but the World Health Organization's (WHO) landmark clofibrate trial demonstrated increased adverse events, especially a rise in noncardiac mortality.[25] However, current therapies for cardiovascular prevention, such as statins, have more favorable risk-benefit profiles[26] and a relatively low cost. For example, in Canada, generic statin medications range in price from US$0.20 to $0.40 per tablet, which is more expensive than in many other countries. Inexpensive medications with a low risk of harm, together with rising rates of chronic disease risk factors,[27,28] have been critical to the medicalization of prevention. This trend has culminated in the development of a "polypill," a combination agent containing a low dose of antihypertensives, statins, and other cardioprotective drugs, which may be a cost-effective and efficient strategy for the primary and secondary prevention of cardiovascular disease.[29,30] Attempts were made to include the polypill in the WHO's Model List of Essential Medicines for the secondary prevention of cardiovascular disease; however, the WHO rejected the applications, citing insufficient evidence for the polypill's efficacy, safety and cost-effectiveness.[31] Whether the polypill can or should be implemented at a population level is uncertain.

Critics argue that the expanding indications for pharmacotherapy through broader definitions of disease, which are often based on industry-funded research, are tantamount to "disease mongering."[32,33] In addition, including more people in the "high risk" category results in treating individuals with a small risk and less potential for benefit.[34] The expansion of eligibility criteria for medication often depends more on the fidelity of risk prediction equations. Recent statin guidelines, for example, were found to rely on risk equations that systematically overpredicted cardiac risk.[35] Expanding indications for therapy also have had a markedly different impact on socioeconomic and race groups.[36] For example, two-thirds of the Americans who are newly eligible for statins under the updated guidelines have no insurance, have a lower income, have less education, and/or are nonwhite. The population impact of these medications will be limited if the causes of treatment disparities, such as the lack of health insurance coverage, are not addressed.

Developments in Nutritional Research: From Isolated Nutrients to Dietary Patterns

PREDIMED Trial

In 2013, a major Spanish clinical trial, Prevention with Mediterranean Diet (PREDIMED), studied the impact of the Mediterranean diet on the primary prevention of cardiovascular disease. PREDIMED randomized patients at high risk for cardiovascular disease to follow either a Mediterranean diet, supplemented with olive oil or nuts, or a control diet based on reducing the consumption of all types of fat, which was the typical recommendation at the time from major disease prevention societies such as the American Heart Association (AHA). The Mediterranean diet is centered on fresh fruits, vegetables, legumes, nuts, olive oil, and a moderate intake of fish and wine.[37] The results of this trial were striking, with the patients on a Mediterranean diet having significantly lower rates of myocardial infarction, stroke, and cardiovascular death, with a relative risk reduction of approximately 30%.

PREDIMED was criticized for the control group's relatively high fat intake, which was more than that recommended in the AHA's guidelines for a low-fat diet (< 30% of total calories from fat).[38,39] Others cited the imbalance in baseline characteristics between the treatment and the control groups despite randomization, as well as concerns that the trial's early termination may have exaggerated the size of the intervention's effect.[40] But PREDIMED is notable in that it is the only trial in primary prevention to demonstrate that a nutritional intervention could lower cardiovascular events and mortality. Both the PREDIMED trial and the Lyon Diet Heart Study,[41] a secondary prevention trial published in 1999, support a paradigm shift toward emphasizing the importance of overall dietary patterns in cardiovascular health. These clinical trials are cited as promising advances in a field mired in controversy over spurious associations resulting from an overreliance on observational data.[40]

Moving Beyond Single Nutrients to Whole Diet

The relationship between diet and chronic disease has been studied intensively during the past 2 decades.[42-45] During this time, there has been a movement away from a focus on isolated nutrients toward examining the influence of specific foods and overall dietary patterns on disease. The

focus on isolated nutrients in dietary recommendations emerged in the mid-20th century with the discovery of diseases resulting from single nutrient deficiencies, such as rickets (vitamin D), beriberi (thiamine), and pellagra (niacin).[46] In the context of cardiovascular disease, the single-nutrient paradigm resulted in research focusing on saturated fats and cholesterol, an approach reflected in nutrient-focused guidelines recommending a limited intake of these dietary components.[41,42]

Research on the association between Mediterranean dietary patterns and cardiovascular disease has a long history, most notably Ancel Keys's Seven Countries Study.[47,48] This was a prospective cohort study that was initiated in 1958 and demonstrated large differences in dietary patterns, cardiovascular risk factors, and rates of coronary heart disease across the United States, Italy, Greece, Yugoslavia, Finland, the Netherlands, and Japan. Improved cardiovascular health and longer life expectancy were observed in populations in Greece and southern Italy, and these outcomes were thought to be associated with the traditional dietary patterns from these regions, the "Mediterranean Diet."

Recognition of the importance of dietary patterns has broad implications for public health and health policy. According to a recent study by the US Burden of Disease Collaborators, dietary risk factors remain the most significant contributor to death and disability in the United States and were found to be associated with 26% of deaths and 14% of disability-adjusted life years.[49] US dietary guidelines already recommend a Mediterranean-style diet for cardioprotection based on observational studies,[50] and PREDIMED offers further support for this recommendation. Other national guidelines, such as Brazil's food-based dietary guidelines, have made a more radical shift in emphasizing the importance of whole dietary patterns, stating that "diet is more than intake of nutrients,"[51] with specific reference to the Mediterranean diet.

Important questions about the Mediterranean diet remain, including the benefit of "Mediterranean" supplements (ie, olive oil and nuts) in a "Western" diet, challenges in the implementation of this diet, and cultural factors that may limit its uptake. Fresh produce, high-quality fats, and seafood are expensive compared with less healthy foods,[52,53] thus making cost a barrier to adherence.[54] A cost-utility analysis by Dalziel and colleagues suggested that a Mediterranean diet may be cost-effective (but not necessarily affordable) for patients with previous myocardial infarction, but cost-effectiveness has not been established for primary prevention.[55]

Major population-level changes in diet would require significant societal changes. Global agriculture and food production are being increasingly consolidated into large transnational corporations, which are able to sell food at lower costs through economies of scale and control over an entire production chain.[56] This industrial model of food production incentivizes the substitution of cheap, lower-quality ingredients (sugar, salt, low-quality fats and oils) to increase profit margins and aggressive marketing to promote overconsumption of energy-dense foods to boost sales.[56] The lower cost of unhealthy, processed food in the United States may also be exacerbated by agricultural subsidies for commodity crops such as corn versus other fruits and vegetables.[57] The impact of these subsidies has been debated,[58] however, with one study suggesting that they have had a minimal effect on increasing overall caloric consumption.[59] Education campaigns and dietary guidelines may be more effective if paired with changes in the production and marketing of healthier foods and taxes or subsidies to incentivize healthier consumer choices.[52,60]

As emerging research emphasizes the importance of broad dietary patterns, multiple policy approaches may be needed. Some current policies attempt to shift populations toward consuming healthier foods through a single-nutrient paradigm. For example, sales taxes on sugar-sweetened beverages may decrease calorie intake and improve health outcomes, and have an indirect benefit through the investment of tax revenues in public health initiatives.[61] In Mexico, the implementation of an excise tax equivalent to $0.055 per liter of sugar-sweetened beverages led to an 11% increase in the price of soda and a 7% decrease in per capita sales of sugar-sweetened beverages.[62] Some policies have targeted broader dietary patterns. Subsidies for fruits and vegetables resulted in a 2% to 5% increase in fruit consumption in the United States[63] and may have averted 6,000 deaths in the United Kingdom.[64] The relative population health impact of taxes or subsidies on isolated nutrients versus policies to shift overall dietary patterns requires further research.

Expensive Medicines: A Cure for Hepatitis C?

Direct-Acting Antiviral Agents for Hepatitis C

The development of remarkably effective treatments for hepatitis C virus (HCV) infection are among the most significant recent breakthroughs in

medical science. HCV is a significant cause of morbidity and mortality affecting 200 million people worldwide,[65,66] with the greatest country-level burden in Egypt, where 1 in 10 individuals is infected as a legacy of schistosomiasis treatment campaigns with unclean needles.[67,68] In the United States, HCV was responsible for an estimated 20,000 deaths in 2014, making it the single greatest cause of infectious death, more than all other causes combined, including HIV, tuberculosis, and pneumococcal infections.[69] These new treatments, known as direct-acting antiviral agents (DAAVs), function by interacting directly with HCV proteins to prevent viral replication.[70]

The ION-1 trial, published in 2014, is one of several studies that demonstrated the marked efficacy of DAAVs for the treatment of HCV infection.[10] Older, interferon-based treatment regimens achieved cure rates of around 40% for the most common genotype and were associated with significant side effects, such as influenza-like symptoms, often resulting in the discontinuation of treatment.[71-73] ION-1 assessed a combination of 2 DAAVs, ledipasvir and sofosbuvir, in patients with previously untreated chronic HCV genotype 1 infection. These drugs far surpassed previous therapies in efficacy and were associated with fewer drug toxicities, with rates of sustained virologic response (which is equivalent to "cure" in hepatitis C infections) of 97% to 99%.

The response to DAAV regimens is variable, depending on the HCV genotype;[70] for example, genotype 3 responds far less well to DAAVs.[74] These differential cure rates based on genotype have important implications for treating the global HCV epidemic. Most advances in the use of DAAVs apply to genotype 1; other genotypes have been less well studied.[75] Non–genotype 1 HCV is more prevalent outside the United States and Western Europe, and genotype 3 HCV is more prevalent in populations using intravenous drugs.[75-77] "Pan-genotypic" treatments that are equally effective against all genotypes are currently in late-stage development. This would be a major advance, as it would eliminate the need for pretreatment genotype testing, which is unavailable in many resource-limited settings and poses a barrier to care.[75,78]

Expanding Medication Costs: Implications for the Treatment of a Common Disease

The medical and public health communities responded enthusiastically to the results of ION-1 and other HCV trials, given the possibility of an

effective "cure" for hepatitis C.[79,80] Cost, however, may limit the impact of these new therapies. A 12-week course of sofosbuvir is estimated at around $84,000, which is prohibitive for most individuals who lack health insurance and could bankrupt public health systems in settings with high prevalence of HCV. Despite the high cost of patented medications, a recent study found that generic forms of these drugs could be produced for $100 to $250 per treatment course.[81] Lower costs could help improve access to these medications in low- and middle-income countries, which bear more than 80% of the worldwide burden of HCV infections. The US patents for these drugs do not expire until 2026–2029, and projections suggest an additional 6 million to 7.5 million people would die from HCV infections before generic production could begin.[79]

Parallels have been drawn between the global HCV and HIV epidemics in terms of the economic and ethical challenges raised by providing access to expensive medications.[80] In the case of HIV, access to antiretroviral therapy was initially limited by high medication costs, and the pharmaceutical industry was heavily criticized as millions of people worldwide died due to lack of treatment. A combination of concerted activism, international funding, and global and national policymaking, along with cooperation from industry, resulted in increased access to therapy. Consequently, an annual course of antiretroviral treatment, which cost around $20,000 in the mid-1990s, became available in some countries for less than $100.[80]

There is some cause for optimism with respect to improving lower-income countries' access to DAAVs. New HCV drugs were recently included in the WHO's Model List of Essential Medicines, which has been identified as a crucial step toward improving access.[82] Indeed, the inclusion of antiretroviral HIV drugs on this list was key to improving access to these medications.[80] Furthermore, the US pharmaceutical company Gilead Sciences, the maker of sofosbuvir, recently approved production of a generic form of this medication for distribution in selected low- and middle-income countries.[83] Nonetheless, critics argue that this move does not go far enough to ensure access to these medications, as many countries with high burdens of HCV were excluded from receiving the cheaper generic forms.[84]

Another reason for optimism is that HCV infection does not require lifelong therapy, and treatment durations are generally only 12 weeks, which will help limit overall costs. Unfortunately, this is not the case for many new therapies being developed for other chronic diseases or

for infectious diseases such as HIV. For example, PCSK-9 inhibitors are novel biological agents to treat dyslipidemia at a cost of approximately $15,000 per year and would be used for lifelong treatment.[85,86] The examples of DAAVs and PCSK-9 inhibitors illustrate how the price-inelastic demand for medications and the drug companies' monopoly pricing power can result in expensive treatments that can be paid for only by third-party payers (ie, governments and insurance companies), which has a substantial impact on total health care expenditure.[86]

Research on the Human Microbiome

Fecal Transplant for Clostridium Difficile *Infections*

Research on the role of commensal microbiota, the "human microbiome," in health and disease has made significant advances over the past decade and is a promising area for translating knowledge from basic science to clinical medicine.[87] Microbes make up our bodies in an approximately 1:1 ratio with human cells,[88] and they play crucial roles in metabolism and immunity, among other functions that are only beginning to be understood.[87,89] One of the most successful clinical applications of research on the human microbiome is the treatment of *Clostridium difficile* infection. *C. difficile* infection is a major global health care challenge,[90,91] and it is the most common hospital-acquired infection in the United States, with 453,000 cases reported in 2011, and 29,000 associated deaths.[92] It is associated with significant health care costs, with an annual expenditure of approximately $1.5 billion in the United States and €3 billion in Europe.[93,94] The microbiome plays a crucial role in *C. difficile* infection, which most commonly results from disruption of native gut microbiota by antibiotic therapy.[92] Suppressing the native flora enables pathogenic *C. difficile* spores to germinate and proliferate, producing exotoxins that cause inflammation and diarrhea. Given this mechanism of *C. difficile* infection, fecal microbiota transplantation (FMT) from individuals with "healthy" colonic bacteria was proposed as a means of normalizing the bacterial composition of the gut and eliminating infection.[95]

The idea of fecal transplantation for *C. difficile* is not new, with the first application reported in 1958.[96,97] However, data from RCTs

studying this intervention emerged only recently, in parallel with the basic science explaining the underlying mechanism. The first RCT studying FMT was conducted in the Netherlands by van Nood and colleagues and published in 2013.[11] This trial enrolled patients with recurrent *C. difficile* infections and randomized them to receive either FMT or oral vancomycin (the standard antibiotic treatment for relapsed or severe *C. difficile* infection). The results of the trial were striking: a cure after 10 weeks was observed in 94% of the patients who received FMT versus 31% who received vancomycin. This study also showed that FMT recipients experienced significant and sustained increases in microbial diversity, becoming indistinguishable from healthy donors following treatment. That is, recipients had increases in bacteria that matched those found in donors' feces, suggesting that donor engraftment was a key mechanism in preventing a *C. difficile* relapse.

Although FMT is an example of successful translational research, several barriers prevent its widespread adoption. The mechanism of delivery of FMT often requires the infusion of donor feces into the small intestine via a tube inserted through the recipient's nose, a relatively invasive treatment protocol, which is being improved through newer innovations such as capsulized forms that can be taken orally like standard medication.[11,98] The widespread use of FMT also may require banking fecal material from a pool of anonymous screened donors, creating an infrastructure analogous to that of tissue or blood donation systems. New developments of monoclonal antibodies against *C. difficile* exotoxins may eventually reduce the need for FMT,[99] but the use of FMT remains a notable milestone in clinical medicine as the first broad application of microbiome-based therapy.

Harnessing the Human Microbiome to Improve Population Health—An Emerging Paradigm

As basic science and clinical research on the human microbiome advance, population health researchers have an important opportunity to engage with this research paradigm using methods such as widespread microbiome sampling, genetic sequencing, and metabolic analysis to address questions related to public health.[100] For example, differences in the microbiome in human populations might provide insights into susceptibility to environmental or infectious agents, as well as geographic

variations in the incidence of disease. Methods for studying the human microbiome may also provide tools for epidemiologists and public health researchers to track geographic changes in microbial composition, such as the response to the introduction of treatments like antibiotics.[100]

Research on the human microbiome may ultimately lead to widespread interventions that extend beyond *C. difficile* infections. FMT is now being used to treat other gastrointestinal diseases, such as inflammatory bowel diseases[101] and patients colonized with multidrug resistant bacteria.[102] These microbiome-based approaches may become increasingly important as the medical and public health communities seek alternatives to antibiotic therapy in an age of increasing resistance.[103,104] While *C. difficile* and other gastrointestinal infections are the prototypical diseases understood to result from disturbances in the microbiome, emerging evidence for the role of microbiota in other disease states, such as cancer, atherosclerosis, and lung disease,[89,105] provides hope that further research in this area will enable novel preventative and therapeutic approaches.

Targeted Therapies in Oncology: The Promise and Limitation of Precision Medicine

Precision Immunotherapy for Metastatic Melanoma

Novel targeted therapies in the field of oncology are at the vanguard of "precision medicine," an approach to clinical care that aims to tailor therapy to specific individuals.[106,107] Some of the most promising "precision" treatments in oncology are small molecule inhibitors and monoclonal antibodies targeted at cancer proteins with specific underlying mutations.[108-110] Another related therapeutic development in oncology is precision immunotherapy, which upregulates the immune system's activity against cancer cells, thus enabling the body to more effectively attack and eradicate the malignancy.[12]

Several highly cited clinical trials demonstrated the efficacy of precision treatments to treat lung cancer, breast cancer, and melanoma.[12,108-110] An RCT by Larkin and colleagues[12] tested 2 immunotherapies in advanced melanoma, ipilimumab and nivolumab,

and found that this combination significantly improved progression-free survival to 11.5 months, compared with a median progression-free survival of 1.7 months for untreated patients.[111]

This trial also illustrated the importance of targeting these treatments to specific tumor characteristics, that is, precision immunotherapy.[112] Nivolumab was designed to block the PD-1 ligand (PD-L1), the mechanism that some cancers use to escape the destruction of the immune system, and a greater progression-free survival was observed in patients with tumors expressing PD-L1. This precision approach stands in contrast to conventional chemotherapy, which utilizes nonspecific cytotoxic agents to destroy rapidly proliferating cancer cells and thus affects other rapidly dividing cells in the body, like hair, skin, and intestinal lining.

The precision therapy paradigm has led to new trial designs, in which treatment is allocated to specific genetic mutations, rather than the standard approach based on tumor location and pathology.[113,114] This represents a significant shift in our understanding of cancer, which is currently primarily categorized anatomically (eg, breast, lung, and colon cancer). While early trials produced underwhelming results,[115] further studies such as the US National Cancer Institute Molecular Analysis for Therapy Choice (NCI-MATCH) trial are under way to investigate the efficacy of molecularly targeted treatments.[113,116,117] The US Food and Drug Administration recently approved the first "tumor agnostic" medicine in this class, pembrolizumab, which may be beneficial across a range of solid tumors that share common genetic features of high microsatellite instability or mismatch-repair deficiency.[118]

Precision Medicine—How Will It Impact Population Health?

Precision medicine has gained significant momentum in recent years and now is a major focus of national science policy in the United States.[106] In 2015, President Barack Obama launched the Precision Medicine Initiative, which pledged $215 million to research in this area.[119,120] Critical voices have emerged, however, highlighting the scientific and pragmatic limitations of this research paradigm in terms of clinical and public health impact.[121-125] Clinical applications have been limited by the ability of genomic analysis to identify "driver mutations," that is, the mutations that are ultimately responsible for tumor proliferation

and thus are the targets of treatment.[120] Additional issues such as tumor heterogeneity (cancer cells within a given tumor can demonstrate variations in gene expression) pose a further challenge to tailoring therapy through genetic markers. Finally, drug toxicity of these novel agents can be significant, as observed in clinical trials.[12]

Public health researchers have argued that the significant allocation of resources to precision medicine distracts from the social-structural factors responsible for health inequities.[124] Precision medicine privileges genetic-level causation and may lead to the relative neglect of environmental and social determinants of health, which may have a greater impact on overall population health.[123,125] Currently known genetic factors have relatively small effect sizes in most cases, especially for common noncommunicable diseases.[121,123] Because precision therapies and diagnostic techniques come at such a high cost and with marginal benefit, rigorous cost-effectiveness analysis is required before they are deployed on a population scale.[120,121]

Comparative effectiveness research on precision medicine has been limited, and further work is essential to guide health policy.[126] A specific challenge in the application of comparative effectiveness methods to precision medicine is the assessment of "personalized" treatments using accepted population-based methodologies.[127,128] For example, it may not be possible to perform RCTs to evaluate therapies targeting rare genetic variants, leading regulatory agencies to use alternative approaches for drug approval (often relying on mechanistic evidence).[129] Comparative effectiveness research is crucial to comparing the role of precision medicine with that of conventional clinical or public health interventions. Research has suggested that social and public health spending may provide greater aggregate benefit for population health than direct health spending does,[130,131] and this may be especially relevant for the expensive and individually tailored treatments offered by precision medicine.

Despite these challenges, precision medicine may also present an opportunity for public health. Initiatives that pair precision medicine with epidemiologic research may produce more robust prediction models by adding data on environmental and social context to genetic profiling.[122] Khoury and colleagues argue that "for precision medicine to succeed, a population perspective is needed" and that population health sciences must play a key role to ensure that advances in precision medicine benefit population health in an equitable and cost-effective manner.[122]

Precision medicine approaches may also be promising for "precision prevention."[122] For example, widespread use of genetic biomarkers may allow for tailoring of screening programs, an approach already being used for diseases such as breast cancer.[122,123,132] Precision medicine's focus on epigenetic and genetic biomarkers, and the increasing affordability and availability of genomic technologies, may have important applications for public health by improving our ability to study the natural history of disease and to understand disparities in population health.[122] Whether such data can be used in the real world to mitigate risk through behavioral changes or health care interventions is uncertain.[121,123]

Discussion

In this article, we reviewed recent themes in clinical research and their implications for population health and public policy. We conclude by discussing crosscutting issues that bridge the themes identified above. These issues include (1) the blurring distinction between clinical and population health interventions, (2) the impact of clinical innovations on health disparities and vulnerable populations, and (3) the financial costs of medical advances and their impact on other forms of social and public health spending.

First, a major theme in our article is the intersection between populationwide strategies to improve health and more targeted interventions. This distinction is central to Rose's population strategy versus high-risk strategies for disease prevention.[22] Major advances in clinical medicine, however, have blurred the distinction between these approaches, as seen with the newest blood pressure and cholesterol treatment guidelines.[6,7] The traditional population health approach to chronic disease prevention through structural and social change needs to be reframed to account for the reality of a medicalized population in which nearly half of the adult US population is eligible for pharmacotherapy.[14] Medication may be an effective means of controlling high-prevalence chronic disease, given that the implementation of population strategies has been limited and evaluation to prove efficacy has been challenging. For example, despite extensive research and policy interventions to reduce obesity rates, no country has yet been able to reverse the obesity epidemic.[133] In addition to underlying structural factors, the lack of any medical therapy for obesity that can be applied at the population level may be one reason why

population-level prevention has not succeeded in lowering obesity rates in high-income countries and in slowing their rise in many low- and middle-income countries.[27] Contrast this with hypertension, for which the development of effective medications has helped control population-level blood pressure,[134] and also with mortality rates of cardiovascular disease, which have dropped substantially with advances in medical therapy.[135] Medication-based interventions may rely less on individual agency than do approaches targeting broader health behaviors such as exercise or diet, and therefore they could be effective in reducing health inequalities if applied in conjunction with efforts to address underlying structural factors that drive differential access and use of medication.

Precision medicine may also blur the distinction between Rose's population strategy and high-risk strategies. While precision therapy may represent the pinnacle of targeted interventions, the emerging idea of "precision public health" leverages knowledge from precision medicine to develop a population strategy for prevention that utilizes population-level genetic and epigenetic data to better understand the environmental factors that contribute to disease incidence.[122] Khoury and colleagues described the similarities between these approaches: "If precision medicine is about providing the right treatment to the right patient at the right time, precision public health can be simply viewed as providing the right intervention to the right population at the right time." The health impact, financial costs, and ethical implications of populationwide applications of genomic technologies require further study.

Second, at a time of rising health disparities,[136,137] it is important to consider not only the impact that new technologies will have on overall population health but also the potential effects on health inequalities and vulnerable populations. For example, earlier initiatives such as cervical cancer screening and smoking cessation campaigns have been shown to preferentially benefit individuals of higher socioeconomic status, thereby widening health disparities.[138,139] Likewise, the application of new cholesterol or blood pressure guidelines may worsen health disparities because of treatment gaps related to socioeconomic status, race, and access to health insurance.[36] Even in countries like Canada with public health coverage, unequal access to specialty care and procedures is associated with health disparities among socioeconomic groups.[140,141] Studies examining the introduction of highly active antiretroviral therapy for HIV demonstrated that the provision of cost-free medications alone was insufficient to reduce unequal health outcomes for groups of

lower socioeconomic status, suggesting that other factors such as access to medications and adherence to treatment regimens contributed to persistent inequalities.[142-145] This lesson from the HIV epidemic is particularly salient given the enormous strides in HCV treatment, and the important barriers in access to medication for groups with low socioeconomic status and in low-income countries where the majority of HCV patients reside. Initiatives geared toward improving access to therapy must be paired with campaigns to address the structural factors that prevent disadvantaged groups from engaging with health care or receiving treatment. This includes participatory initiatives that engage local communities while recognizing and respecting the socially and culturally specific determinants of health for particular marginalized peoples.[146,147]

Third, another important issue raised in our article is the financial cost that would be associated with the implementation of medical advances. Even though the annual individual cost is relatively low for statins and many blood pressure medications,[148] the lifelong use of these therapies by nearly half the American population would result in enormous costs to the health care system. The use of DAAVs for HCV would also have significant system costs because of the very high individual cost of treatment combined with a prevalence of HCV that is as high as 10% in countries such as Egypt.[68] These therapies could also produce cost savings for health care systems by preventing myocardial infarctions in the case of statins and antihypertensives, or complications of HCV (such as cirrhosis and hepatocellular carcinoma) in the case of DAAVs. Population-level cost-benefit analysis is required as new indications and new therapies are developed.

The use of FMT would require the type of infrastructure that has been built for blood transfusion services, for which the on-demand provision of a biologic product requires resources for collection, screening, storing, and distribution. Precision medicine requires extensive financial investment for research and development, and precision therapies that have gained regulatory approval are among the most expensive medications used in clinical practice.[121] Finally, whole-scale changes in diet on the population level necessitate a fundamental alteration of our model of food production, marketing, and distribution, which would essentially be a transformation of one entire pillar of the modern economy. Collectively, these examples illustrate that the societal disruption and financial costs associated with the implementation of medical advances are substantial. In single-payer health systems in which health care costs already are a

high percentage of total tax revenue, the further expansion of health care costs may require increasing taxation rates or reallocating other public resources. In private payer–based systems, expensive therapeutics will undoubtedly drive further inequalities in access to high-quality health care.

Our article has several limitations. Despite our selection of high-impact general medical journals, the articles we reviewed focused on conditions related to internal medicine and thus may be less representative of developments in, for instance, pediatrics, mental health, and surgery. The journals we selected do publish the highest-impact research in these non–internal medicine fields, and therefore our article selection may reflect a greater focus on and more resource allocation to internal medicine within clinical research. We organized our literature search according to the number of citations, a metric that offers only a surrogate measure of impact not necessarily reflective of the actual clinical impact of a trial or predictive of a study's future influence. Furthermore, there is a bias toward selecting articles published earlier during the time period examined. Our analysis of the most-cited articles identified several themes, not all of which we were able to explore here. Notable themes not discussed include trials on endovascular treatment of stroke[149-152] and studies of HIV pre-exposure prophylaxis.[153-155] Our assessment of clinical novelty and impact was based on whether an article or theme changed the understanding/paradigm of disease, and we acknowledge that there are other definitions/approaches to determine this. For example, although endovascular therapy for stroke represents an important clinical therapy,[149] the published studies represent a refinement of existing therapeutic paradigms regarding ischemic stroke, such as the use of tissue plasminogen activator[156] or the application of techniques already being developed for similar disease models, like thrombectomy for myocardial infarction.[157] Accordingly, we did not discuss the theme of thrombectomy for stroke. We recognize that the impact on clinical and population health is difficult to predict and that the criteria we used for selection are subject to differing interpretations based on authors' views and opinions. Our article, therefore, is not a systematic or comprehensive review of recent clinical literature but rather represents our perspective, as experts in clinical, population health, and health services research, based on a thorough review of high-impact studies that we believed would be informative for nonclinicians. Another limitation of our article is that we do not provide a comparative effectiveness analysis of the populationwide and targeted interventions discussed, as the data to make

these comparisons are not currently available. Such an analysis is indeed crucial to inform health policy. Despite these limitations, we hope that this article will stimulate an interdisciplinary dialogue about the population impact of novel technologies and how they might be implemented in a manner that ensures more equitable and cost-effective access.

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