Insights from the IBD Prevention Workshop

Executive Summary

At the Inflammatory Bowel Diseases (IBD) Prevention Workshop at The Royal Danish Academy of Science and Letters in Copenhagen on March 5, 2019, leading stakeholders from public, private, and nonprofit institutions gathered to discuss research in IBD and the steps necessary to achieve IBD prevention. Critical research gaps were identified, including the need to better understand the natural history of the two major forms of IBD: Crohn's disease and ulcerative colitis, especially in early stages, for preventive intervention. It was agreed that nomenclature and definitions regarding pre- or sub-clinical disease stages need to be established, along with risk stratification of multiple distinct disease phenotypes. Other topics discussed centered around whether current diagnostic criteria need to be updated, particularly in anticipation of efforts to develop primary prevention strategies. Questions were raised about when to intervene, and whether it would be possible and appropriate to administer preventive measures before the onset of disease. This would of course rely on the discovery of robust predictive biomarkers. In turn, the identification of at- or high-risk individuals is not useful unless intervention is possible. The requirements for effective intervention were duly discussed and updates were shared regarding ongoing studies and registries in IBD. Experts researching other immune-mediated inflammatory diseases, namely type 1 diabetes, systemic lupus erythematosus, rheumatoid arthritis, and coeliac disease, added their opinions and experience regarding pivotal stages in the advancement of their respective research fields and how IBD research may be expedited to achieve similar milestones. Other important takeaways were that standardization of methods across studies would add value by facilitating both meta-analyses and cross-validation. The coordination of workflows would allow studies to function more closely in parallel and complement, rather than in linear, step-wise ways, to maximize efforts while reducing redundancies in work. The meeting not only highlighted the need for greater collaboration but enabled attendees to identify opportunities to share knowledge and practice, as well as develop closer working relationships and better cross-study/registry coordination. At the end of the workshop, the attendees collectively agreed on the key steps needed to advance the field towards prevention of IBD onset and/or progression in individuals at risk of, or living with, IBD.

Introduction

Like many other immune-mediated inflammatory diseases (IMIDs), inflammatory bowel disease (IBD) has a pre-clinical period when immune, metabolic, and microbiome-driven pathways are dysregulated prior to the overt manifestation of disease symptoms. Understanding the critical early events that take place before disease onset, diagnosis, or progression could lead to the development of predictive algorithms and strategies directed at the prevention of Crohn's disease (CD) and ulcerative colitis (UC), the two major forms of IBD. To this end, over 50 experts and stakeholders from the IBD and other IMID research communities were convened for the IBD Prevention Workshop at The Royal Danish Academy of Science and Letters in Copenhagen on March 5, 2019, with the aim of discussing their latest research and sharing lessons learned, in order to collectively determine the necessary steps for the prevention of IBD.

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Definition of Pre- and Sub-Clinical Disease

It was generally agreed by all attendees that gaining a better understanding of the natural history of IBD, especially during its early stages, would be essential for the development of therapies, particularly preventive ones. This was the case for other IMIDs, such as type 1 diabetes, which can now be predicted relatively well, and as such, has enabled the field to shift from managing 'frank' disease, which refers to advanced disease with full-blown inflammation, towards disease prevention. Critical to understanding the very early course of IBD is the nomenclature and definition of the early stages of the disease. This is also relevant for stratifying disease risk, as well as for determining the disease stage at which prophylactic interventions should be administered. Until this point, the terms 'pre-clinical' and 'sub-clinical' have been used to define CD in its early stages, but there has not

been universal agreement in how these terms should be used. Better refinement of these two stages is needed, but for now, it was suggested that they could be distinguished as follows: pre-clinical IBD occurs before sub-clinical IBD and is marked by the presence of risk factors and predictive biomarkers. Sub-clinical IBD occurs after pre-clinical IBD and is marked by signs of disease that are below the diagnostic threshold. Sub-clinical IBD can be inferred from elevated levels of calprotectin in stool, whereas reliable biomarkers are still needed to accurately detect pre-clinical IBD.

Studies of healthy first-degree relatives (FDRs) of patients with CD, who are at a relatively higher risk of developing CD than the general population, revealed a variety of phenotypes, which could be classified into

Spotlight on an Ongoing Prevention Study: GEM Project

To date, the Genetic Environmental Microbial (GEM) Project has recruited >5,000 first degree relatives (FDRs) of patients with CD who are at increased risk of developing the disease due to shared genetic makeup. The study prospectively monitored these individuals, 87 of which have since developed CD, to study the causes of CD. Preliminary analyses of this unique cohort show that pre-existing abnormal intestinal permeability, decreased intestinal microbial diversity, the altered abundance of several microbial groups, and genetics contribute to the future risk of developing CD.

subpopulations (Sorrentino 2014, Turpin 2019). One study identified three distinct groups based on fecal calprotectin, endoscopic, and histological assessments of 38 FDRs (Sorrentino 2014). One group was healthy with no lesions. Another group had sub-clinical inflammation, indicated by elevated fecal calprotectin levels, which did not progress to disease. A third group demonstrated frank lesions, with inflammation and ulcerations typical of CD. Similarly, the Road to Prevention (RTP) study, led by IBD researchers at the Icahn School of Medicine at Mount Sinai, is identifying high- and low-risk phenotypes – based on serology, microbial composition (fecal and oral),

fecal calprotectin, metabolite composition (serological and fecal), metagenomic composition, human immune response, RNA expression, and exposome (teeth and hair) – in FDRs of patients with IBD prior to the onset of IBD. Another study, the Crohn's and Colitis Canada Genetic Environmental Microbial (GEM) Project, is using machine learning to devise a CD Risk Score, predictive of developing CD, based on several factors, including genotype, intestinal permeability, and microbiome-composition signatures (Turpin 2016, Turpin 2019, Turpin 2020). The CD Risk Score is currently being validated and could prove useful as a surrogate marker for assessing the outcome of preventive interventions. A clear priority that emerged from discussions during the IBD Prevention Workshop was the need to develop clear nomenclature and definitions for disease stages, particularly for pre- and sub-clinical stages, which could be accepted and used across the IBD community.

"Identifying these different risk factors and populations and being able to identify at- or high-risk individuals early enough to intervene is the key to improving outcomes for patients and their relatives."

Risk Determination and Stratification

Genetic predisposition to IBD is indicated by the observation of greater concordance rates of CD and UC in monozygotic twins compared with dizygotic twins (Ng 2012; Halfvarson 2011; Spehlmann 2008; Jess 2005; Halfvarson 2003). FDRs of people with IBD are therefore at a higher risk of developing CD than the general population due, in part, to genetic factors. Within this population, some individuals have no disease while some have sub-clinical lesions that do not progress to disease, and others have sub-clinical lesions that do progress (Sorrentino 2014). It was speculated that individuals with sub-clinical lesions that do not progress to disease may possess the causal disease-associated defect, but may not have incurred a necessary environmental trigger or may possess an additional protective factor that prevents disease progression. Certainly, there is evidence to suggest that environmental factors are at play. Data so far from the RTP study indicate that there are high- and low-risk

phenotypes among FDRs of patients with IBD, with the former displaying a high-risk microbiome signature. An analysis of heavy metals in the baby teeth of a small cohort of adult IBD patients and healthy controls suggested that metal exposure during a critical period in early life may be a risk factor for IBD (Nair 2020). Through studying large Ashkenazi Jewish families with three or more FDRs with IBD, the RTP study has also shown that birth order is important, with affected siblings significantly more likely to be sequential in birth order, as opposed to randomly distributed within the family, as one might expect in a purely genetically inherited disease (Spencer 2020). The clustering of affected siblings suggests non-genetic factors, likely attributable to a shared environment, to be influential in determining the risk of developing IBD.

The Exploring MEChanisms Of Disease TraNsmission In Utero through the Microbiome (MECONIUM) study revealed that not only are there differences in the microbiomes of pregnant women with IBD compared to those without IBD, but the microbiomes of babies born to mothers with IBD, even in remission, are different than those of babies born to mothers without IBD. The differences between the babies persisted for up to 3 months of age (Torres 2020). Other environmental risk factors have also been implicated and an emerging consensus points to urban living as a risk factor for CD and rural living as being protective (Benchimol 2017, Piovani 2019). However, geographic differences were also identified in registry data on IBD incidence, with CD occurring predominantly in agricultural rather than urban areas in Northern France (Gower-Rousseau 2013). Identifying these different risk factors and populations and being able to identify at- or high-risk individuals early enough to intervene is the key to improving outcomes for patients and their relatives.

Diagnosis and Prevention

Current diagnostic criteria for IBD are lacking in accurate, non-invasive indicators that would allow for the detection of disease at early stages. It then follows that consideration should be given to updating the diagnostic criteria to include pre- and sub-clinical, or asymptomatic, individuals. This would enable earlier intervention that could better prevent disease progression or even prevent disease onset entirely. The definition and population targets of primordial, primary, secondary, and tertiary prevention were then discussed. Primordial prevention focuses on attenuating risk factors, and so it is critical

that the environmental, economic, social, and behavioral conditions that can trigger disease be defined. Primary prevention aims to prevent the onset of disease in healthy individuals and will require a better understanding of the disease continuum and the underlying molecular events that characterize the pre-clinical stage. Secondary prevention targets pre- and sub-clinical disease and will require an early diagnosis to halt the progression of disease at an incipient stage to prevent complications. Meanwhile, tertiary prevention targets those individuals diagnosed using the current criteria with measures aimed at reducing the impact of long-term disease by preventing disabilities and complications. It was generally agreed that the earlier the diagnosis, the greater the opportunity to treat the individual and prevent the progression of the disease. Therefore, IBD prevention hinges on understanding the natural history of the disease, which is still not well established.

Biomarkers for Prevention

Early diagnosis of IBD patients is crucial for improving disease outcomes and hence, there is a need for the identification of reliable biomarkers to accurately predict the onset and prognosis of IBD. The development of diagnostic biomarkers also serves to address the issue of misdiagnosis, which is relatively common (Ananthakrishnan 2012). Biomarkers currently used to support a clinical evaluation in the diagnosis of IBD include C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), calprotectin, lactoferrin, anti-Saccharomyces cerevisiae antibodies (ASCA) / perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) profiles, and where testing is available, the calcium-binding protein S100A12 (Iskandar 2012). These biomarkers may not only be indicative of inherited risk factors but, like ASCA, may be markers of specific responses to particular environmental antigens (Halfvarson 2005).

The RTP study aims to develop a predictive biomarker panel based on the discovery of specific genetic, serologic, and/or microbial alterations detected in high-risk individuals prior to the onset of IBD. This should help inform rational preventative or very-early interceptive strategies. The PRoteomic Evaluation and Discovery In an IBD Cohort of Tri-service Subjects (PREDICTS) study applied proteomics analyses to identify antibodies and proteins that are differentially expressed in the serum

PRIMARY
Prevent the onset of illness in healthy individuals genetically predisposed to developing Crohn's disease.

SECONDARY
Detect pre- or sub-clinical biomarkers for early diagnosis and design interventions to delay the onset of Crohn's disease in asymptomatic predisposed individuals.

TERTIARY
Improve treatments and outcomes for patients with established Crohn's disease to delay disease progression and complications.
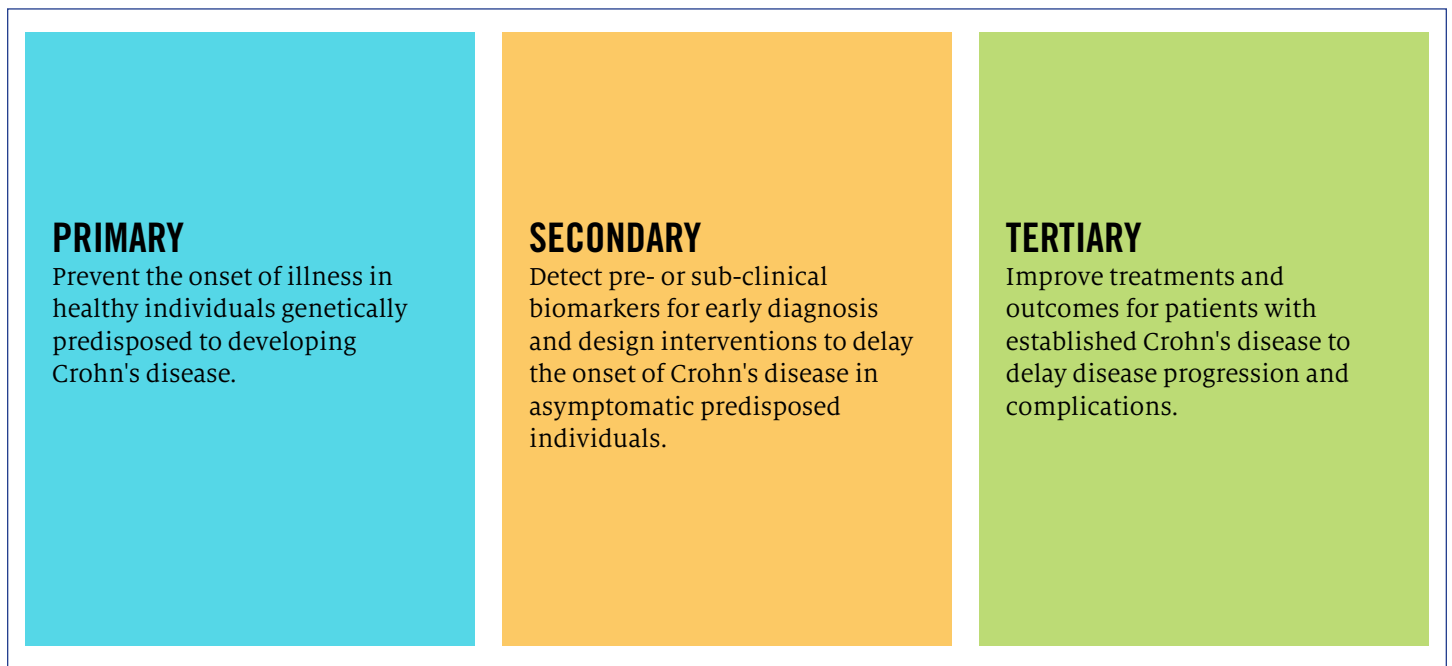
Figure 1. Defining Crohn's disease prevention

of patients with CD compared with healthy controls (Porter 2019). The identified proteins were shown to be predictive of individuals who will receive a diagnosis of CD within the next five years with high accuracy (Torres 2020). Moreover, complementary research identified antibodies and protein markers associated with complicated CD, as opposed to uncomplicated CD (Choung 2019). Such distinction is important in guiding clinical decisions regarding treatment options. Other projects are also underway to investigate candidate predictive biomarkers, such as high sensitivity CRP (hsCRP), interleukin-6 (IL-6) (Lochhead 2016), and testosterone (Khalili 2015), all of which were found to be elevated in the plasma of individuals with IBD prior to diagnosis.

Preventive Interventions

Biomarkers and diagnosis – no matter how early - are meaningless without effective interventions. It was highlighted that there is heterogeneity in response to

Related Study: PREDICTS

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treatment, which may be influenced by the duration of the disease as well as disease severity. Intervening effectively as early as possible in the disease course seems to offer the best prognosis, particularly for patients with CD. There continues to be a need for precision medicine in CD to achieve not only precise diagnosis but also to accurately match therapies to individual patients and thus improve outcomes by providing better, more efficient care at a lower cost. The feasibility of this was discussed. It was agreed that in reality, few diseases can truly be prevented,
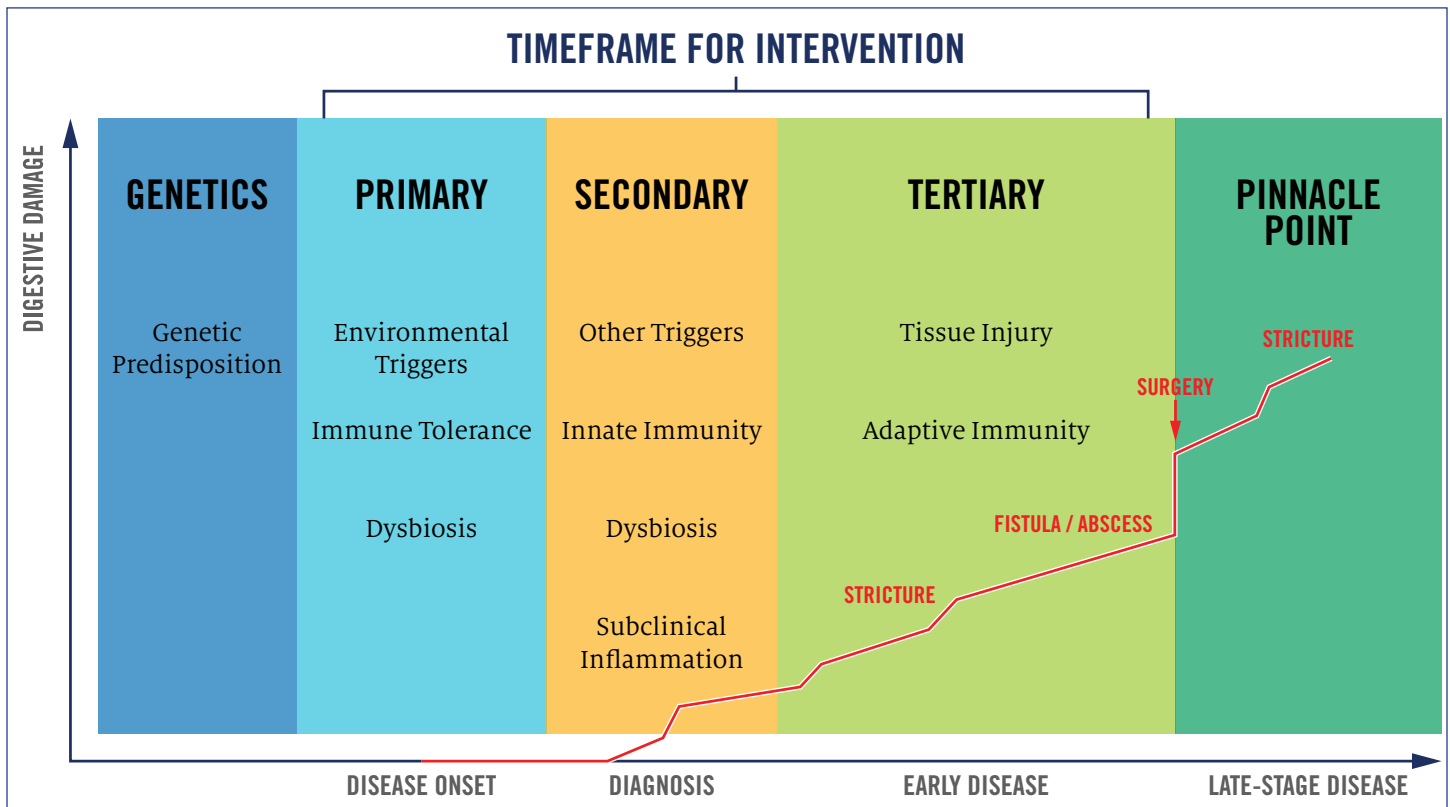

Figure 2. Levels of prevention during the course of Crohn's disease

especially solely through the modification of risk factors. Diagnosis with biomarkers would lead to secondary rather than primary prevention. It was suggested that for CD, aiming for primary prevention may be too ambitious and that only secondary prevention would be possible – at least in the near term. However, it was also agreed that it is primary prevention that is most needed, to reset the immune dysfunction that may cause the disease. Further discussion refined that it is actually "pre-emptive" rather than "preventive" therapy that is required.

The point was also raised that people who are actually healthy tend to be difficult to convince to take medicines or other therapeutic interventions. Adopting a "pre-emptive" approach may make the proposition more attractive because it can be perceived as a "treatment" against the development of IBD, akin to a vaccine. However, experience has shown that it is challenging to motivate people to get tested for a disease or a predisposition to a disease. The balance between benefit and risk always needs to be made, taking into account both the efficacy and safety profiles of potential preventive interventions.

while ensuring that all the critical questions are being answered. In this way, methods and approaches can also be better standardized and organized to optimize the extraction of meaningful information from each project, singly, and in concert. Moreover, assuming a more agile approach where multiple research questions are being studied and answered in parallel means that results could be automatically validated across studies and the research community could respond rapidly and efficiently to study outcomes with the development of new research projects, methods, and approaches.

Lessons learned from members of the other IMID research communities were shared regarding the need to coordinate research efforts and studies, and to identify efficiencies of scale and synergies. Moreover, they unanimously agreed on the overriding importance of understanding the natural history of the disease, as this was the catalyst that enabled the discovery of biomarkers and the development of therapies to not only more successfully treat the IMID, but also to progress towards preventive measures.

Standardization and Workflows in Research

A critical factor and key priority for all attendees was the need to standardize methods for studying IBD. The lack of consensus regarding which markers and surrogate measures to assess generates difficulty in comparing experimental results and datasets and hampers systematic reviews and meta-analyses. This also means that researchers may not be getting the most from their most precious and limited resource: biological samples from patients (and healthy controls). It was proposed that a Working Group be established to standardize and develop methods for studying IBD.

It was also clear that the research community – including academia, nonprofit organizations, and industry – needs to unite in multi-stakeholder collaborations to better deliver and sooner realize effective strategies for IBD prevention for individuals at risk and patients early in the disease process. By working together, efforts and resources can be coordinated to ensure that knowledge gaps are addressed efficiently and that the work is divided up in such a way as to minimize unnecessary overlap

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