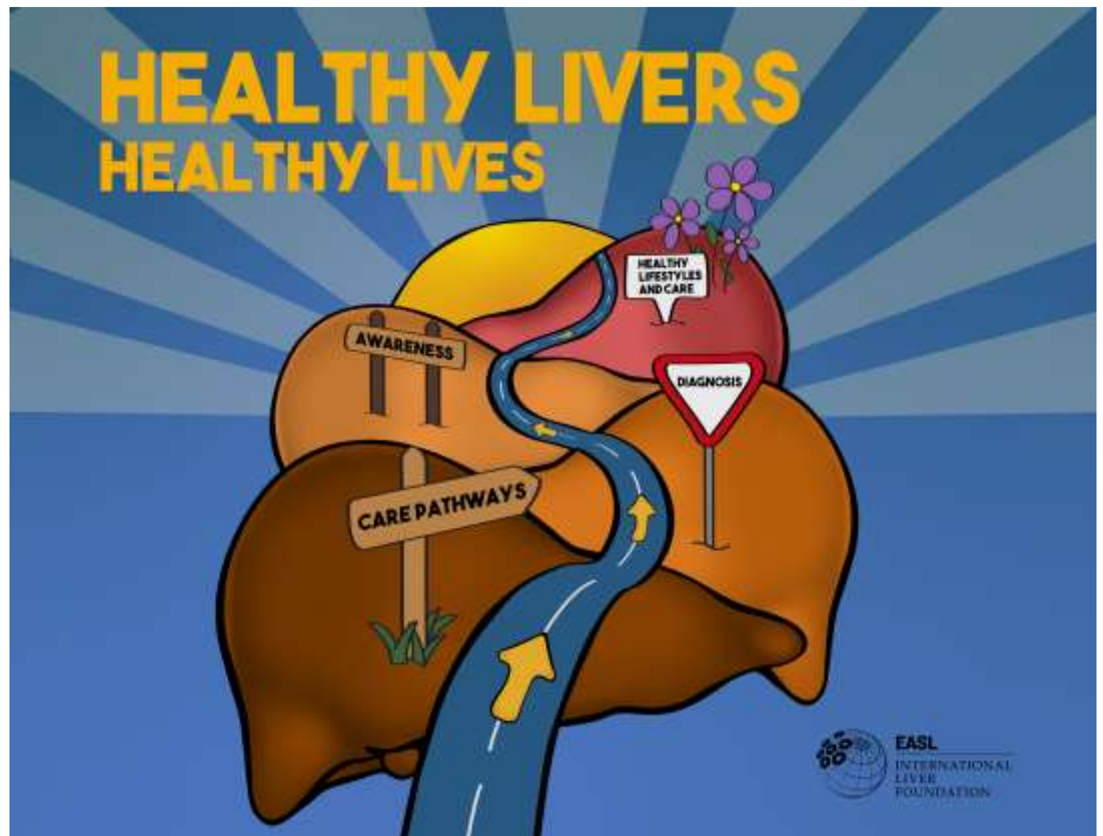

Report

Wilton Park virtual dialogue:

NAFLD/NASH: the silent epidemic

Tuesday 2 – Thursday 4 December 2020 | WP1736V3

In partnership with

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In partnership with the EASL International Liver Foundation (EILF)

Non-alcoholic fatty liver disease (NAFLD) is a rapidly growing global health challenge. Despite affecting around 1 in 4 adults worldwide and causing substantial health and economic damage, NAFLD has received scant attention from public health policymakers, healthcare practitioners and global health experts.

This event was the first of its kind to address NAFLD from a broad global public health perspective, bringing together some 58 thought-leaders, healthcare providers, industry executives and high-level government decisionmakers from 24 countries, covering all regions of the world, to engage in solution-oriented dialogue.

The dialogue built upon several activities led by EILF over the past two years, including a global review of national NAFLD policies, two virtual Wilton Park events on NAFLD care pathways and a series of 12 regional workshops in collaboration with the Economic Intelligence Unit, in Asia, Latin America and the Middle East.

The December 2020 dialogue forms part of a Wilton Park–EILF series which aims to help shape and deliver a coordinated and collaborative response to NAFLD.

Executive summary

- NAFLD is a public health challenge that causes a substantial burden of ill health and economic losses, yet the condition is largely absent within the global health agenda.
- At a health systems level, greater focus needs to be placed on how we orient services around patient needs. NAFLD is closely related to other chronic non-communicable diseases (NCDs). People living with NAFLD often present with multiple comorbidities and require multi-disciplinary management, yet such models of care are not common in many healthcare settings.
- From a public health perspective, action is needed on both the immediate and underlying causes of NAFLD. There is much overlap with existing efforts in the NCD space, including around food systems and urban planning. Understanding points of convergence with other public health efforts will be key for taking action on NAFLD.
- To place NAFLD on the global public health agenda the liver health community must build alliances and actively push for action. A coalition of empowered stakeholders is needed to drive this forward.

Introduction

1. NAFLD is a public health challenge that is global, substantial, complex and invisible. It is the most prevalent liver disease in the world, affecting roughly 1 in 4 adults globally, with serious health, social and economic implications.
2. NAFLD is largely invisible to the general population, policymakers and the public health community – and often even within the field of liver health. Both because and as a result of this, it remains absent from global public health and development agendas, and few countries have taken concrete action to address it.
3. There is a strong association between NAFLD, obesity and NCDs such as diabetes and cardiovascular disease. Addressing NAFLD will require a comprehensive public health response, with collaboration across a variety of health specialties and sectors, from food systems to urban planning.
4. Global stakeholders need to work together to craft a joint vision for addressing NAFLD and to develop a roadmap for achieving this vision at the global, national and local levels. Accordingly, the programme for the present dialogue was specifically designed to inform the development of both a global coalition of stakeholders and a NAFLD public health roadmap.
5. To inform the development of the roadmap, EILF is leading a parallel process to develop a global NAFLD consensus statement that will provide clarity on the priority actions, challenges and opportunities that the roadmap needs to address. An interdisciplinary group of over 200 experts from around 100 countries will follow a Delphi-like process to develop consensus points and recommendations. This work will be published in late 2021.
6. The NAFLD public health roadmap will be a strategic document which outlines how to operationalise the consensus recommendations. Development of the roadmap will require a multisectoral, multi-stakeholder process with policymakers, clinicians, academics, civil society and the private sector all engaged.

The human and economic burden of NAFLD

7. There is a pervasive lack of good disease burden data for NAFLD. The lack of easy-to-use non-invasive tests for NAFLD that can be employed in population-based surveys makes collection of such data challenging.
8. In the absence of comprehensive population-based data on NAFLD and all of its clinical sequelae, the Institute for Health Metrics and Evaluation (IHME) utilizes multiple data sources and regression methods to produce the most precise comprehensive estimates they can.[1]
9. A sharp increase in NAFLD without cirrhosis has been observed since 2005, which will translate to a sharp increase in mortality over a period of 10 to 30 years. It is this significant future burden which policymakers, public health experts and the general public are seemingly unaware.
10. Premature mortality is the primary source of lost health due to NAFLD. NAFLD accounts for approximately 70% of all liver disease, but less than 10% of the

[1] The few available population-based surveys that utilize ultrasound to diagnose NAFL (without liver cancer or cirrhosis) are combined with covariates for population mean BMI, mean fasting plasma glucose, and prevalence of obesity in a Bayesian meta-regression model to predict NAFL prevalence worldwide. Prevalence and mortality due to cirrhosis and liver cancer due to any aetiology are estimated using vital registration and other causes of death data in separate models, and these models rest on the strongest databases. The estimates of cirrhosis and liver cancer are then divided proportionately into multiple aetiologies (alcohol, hepatitis B, hepatitis C, NASH, etcetera). The proportions assigned to NASH are modelled using case-series data (which are scant) and covariates for BMI, obesity, and fasting plasma glucose.

resulting deaths. This is in part due to the slow progression of liver disease and the high risk of cardio-metabolic complications, with cardiovascular disease the leading cause of death in NAFLD patients.

11. Obesity is a major risk factors for NAFLD with the prevalence increasing proportionally with increasing BMI. NAFLD also shares a bi-directional relationship with metabolic syndrome and type 2 diabetes mellitus (T2DM). As the prevalence of obesity and T2DM increase, so will the prevalence of NAFLD.

12. Historically, patient-reported outcomes (PROs) data have not been widely collected as part of the NAFLD research agenda, although this approach has become more mainstream in recent years. Such data can provide important insights into the burden of the disease.

13. There are large health and non-health care costs associated with NAFLD. Recently the GAIN study[2] looked at the socioeconomic burden of NASH to patients in the United States and five European countries. The study showed that indirect costs are substantially greater than direct costs and that quality of life generally worsens with advancing fibrosis. These findings are similar to earlier estimates showing the substantial direct medical costs and social economic burden of NAFLD.[3]

- More and better epidemiological data are needed, including the prevalence of NAFLD by fibrosis stage and the prevalence of NASH. Data are also needed on clinical outcomes, such as liver transplantation, together with improved mortality data, including where NAFLD is an underlying cause.
- Better data on social outcomes–including work productivity and quality of life–will strengthen the economic and emotional arguments for addressing NAFLD. Patient-reported outcome (PRO) data instruments that are locally, regionally and globally validated will be needed to facilitate this.
- Resources should be focused on particular high-risk population groups, especially people living with type 2 diabetes and obesity. Harmonized approaches that facilitate data sharing and comparisons at the national and regional levels will be important as we seek to advance the evidence base. Groups with clinical and PRO data are encouraged to publish it.

Making the case for NAFLD within the global health agenda

14. NAFLD is largely absent within the global health agenda. The World Health Organization (WHO) plays a pivotal role in shaping this agenda, including developing strategies and guidance. However, NAFLD is currently absent from the WHO global action plan for NCDs and other key WHO and United Nations documents.

15. Much of the current prevention and treatment advice for NAFLD dovetails with advice from the WHO and other health organisations on the prevention and management of other NCDs, and there is a large overlap in affected populations. This provides a strong basis to advocate for NAFLD to be part of the NCD agenda within these institutions. Given the significant overlap, at a technical level it would be fairly straightforward to incorporate NAFLD into NCD programmes and guidance.

16. At both a strategic and operational level, much of the focus on NCDs is based

[2] https://www.jhep-reports.eu/article/S2589-5559(20)30076-8/fulltext

[3] https://aasldpubs.onlinelibrary.wiley.com/doi/pdf/10.1002/hep.28785

around the 5x5 framework which outlined five major conditions (cardiovascular disease, chronic respiratory disease, cancer, diabetes, and mental and neurological conditions) and their five common risk factors (unhealthy diets, tobacco use, harmful use of alcohol, physical inactivity, and air pollution). There are, however, signs that thinking on NCDs is moving beyond this framework to consider other conditions. This may provide an opportunity to positioning NAFLD within the NCD agenda moving forward.

17. Affected communities have been pivotal in raising awareness and putting other diseases on the global health agenda, including viral hepatitis, for example. Affected communities have a deep understanding about the impact of diseases. They can help give the disease a human face while being strongly motivated to bringing about change. However, there are currently very few patient groups focused on NAFLD.

18. Individual countries and medical practices can be catalysts for change, most notably by pioneering replicable model for other to follow. Other stakeholders who can play key roles in championing NAFLD include national and regional liver societies, other professional societies, private sector organisations, and even individual clinicians and public health experts.

19. In lobbying for change, advocates are most effective when they address the ‘head, heart and pocket’ simultaneously, focusing on the burden of disease, human-interest stories and the financial impact, respectively. Of these three, appealing to the heart tends to be most persuasive – and most often omitted. Stories about affected children and adolescents can be especially motivating.

20. Increased attention and recognition of NAFLD within global health institutions will help to raise awareness of the issues across different sectors and in the general population, helping to drive much needed action and investment.

- The liver health community must build alliances and actively push for greater recognition and action on NAFLD within global, regional and national institutions. In pursuing these efforts, we should explore how to engage with existing platforms and initiatives, such as the Global Coordination Mechanism for the Prevention and Control of NCDs (GCM/NCD) and the NCD Alliance.
- Pioneer countries should be supported to become flag-bearers for NAFLD. A medium-term goal should be for national delegations to support a resolution at the World Health Assembly acknowledging NAFLD as a public health threat requiring action. This has previously been successful for advancing the viral hepatitis agenda.
- To support advocacy efforts, we require data and communication strategies that target the head, heart and pockets of decisionmakers.
- Issue literacy is the oxygen of successful movements and will be crucial for all NAFLD stakeholders. Thought needs to go into developing knowledge products that increase literacy and involve more people in NAFLD. Infographics and audio-visual content can be powerful approaches to help achieve this.
- The NAFLD community need to find hooks for engaging wider audiences on the issue. Existing health priorities offer a potential entry point. Cancer prevention receives significant attention and NAFLD is becoming an increasingly important cause of liver cancer. Framing NAFLD interventions as cancer prevention may be one powerful way to engage others.

NAFLD, a complex multi-system disease

21. NAFLD shares a complex bi-directional relationship with metabolic syndrome (MetS) and type 2 diabetes mellitus (T2DM). An estimated 70% of those with T2DM have NAFLD, while the incidence of T2DM is two-fold higher in patients with NAFLD.
22. Given the asymptomatic nature of NAFLD, it is commonly detected incidentally in connection with other comorbidities. It can be a challenge to convince patients that it is a separate and important health issue, rather than simply a consequence of these comorbidities. Finding a way to communicate the consequences of NAFLD will be an important part of making the case for greater attention and investment.
23. Everyone working in the area of cardio-metabolic health should be aware of NAFLD, yet it is largely unknown outside of the liver field.
24. Clinical guidelines for NAFLD are lacking in most countries. Regional and national liver associations can help fill the void by developing guidelines that can be use at the national level or adapted to the local context.
25. Given the association between NAFLD, obesity and T2DM, and the need for integrated care, clinical guidelines for these conditions should incorporate NAFLD. This will require cross-disciplinary collaboration.
26. The name 'non-alcoholic fatty liver disease' is problematic from a communications perspective. The name is cumbersome and defines the condition by what it is not, something that the NCD community has historically battled with.
27. There are ongoing discussions around the nomenclature for fatty liver disease with recent proposals for a change from NAFLD to 'metabolic-associated fatty liver disease (MAFLD)' receiving some support. However, disease name changes are complex. Broad consultation is needed to consider all of the direct and indirect implications, including changes required to diagnostic criteria and translation to other languages.

- There is consensus on the need for collaboration on NAFLD among diverse fields, including liver health, general practice, diabetes, obesity, and heart disease. Such collaboration is needed across all areas from basic and translation research to service delivery and advocacy.
- Efforts are needed, including at a research level, to highlight how NAFLD influences a patient's overall health, including the increased mortality risk and decreasing quality of life associated with the progression of NASH.
- Professional societies have a key role to play in initiating cross-disciplinary collaborations and providing leadership on key issues such as the ongoing nomenclature debate.
- Efforts are needed to raise awareness and knowledge in health professionals outside of the liver field. Education tools tailored for specific groups will be needed to support these efforts. Specialists present at the meeting indicated they would take this forward in their own hospitals; these examples may provide models that can be replicated more widely.

Delivering care for people living with NAFLD

28. NAFLD covers a broad disease spectrum with multidisciplinary, collaborative approaches required to deliver care to affected populations. In most settings this will include GPs, nurses, hepatologists, diabetologists, endocrinologists, nutritionists, and other allied health professionals.

29. Patients with advanced fibrosis generally need to be referred for further assessment and care by a liver specialist, while those with early-stage disease can often be manged in primary care.
30. Care pathways with clear referral criteria need to be in place to support the identification and referral of patients who are suspected to have advanced fibrosis. Non-invasive tests, such as blood-based scores and elastography techniques, are the foundation for such care pathways. Ensuring healthcare providers have adequate knowledge of and access to these tests is key to implementing these approaches.
31. A care pathway is a framework for mutual decision-making and as such it should be jointly developed by e.g. primary care providers, liver specialists and payers. These pathways should be based on the local context, including the availability of different diagnostic tests. Where primary care is heterogeneous, pathways need to be flexible.
32. Routine NAFLD screening is not widely employed, even in high-risk population groups, such as people living with diabetes. Barriers to widescale screening include a lack of access to and knowledge of simple diagnostic tools, poor awareness of NAFLD among primary care physicians and limited access to and incentives for comorbidity prevention in many population groups. The absence of NAFLD-specific pharmacological treatments also continues to present a barrier.
33. Proactive case-finding in high-risk groups–namely people living with diabetes and obesity– may be more effective than untargeted screening. Such an approach requires close collaboration with primary care physicians and diabetes specialists.
34. Screening approaches need to be embedded within clinical guidelines including which population groups to target, when to request tests and how to interpret the results. Systems that simplify decision-making processes, such as care algorithms, can help to facilitate the implementation of screening strategies.
35. Given the co-morbid nature of NAFLD, many patients require services from several disciplines. Globally there are some examples of multi-disciplinary clinics where care providers are co-located. However, in many healthcare setting the development of multidisciplinary care models for NAFLD is challenging. Where physical co-location is not feasible, virtual co-location through electronic platforms may provide a solution.
36. Few countries (about 30% globally) have clinical guidelines for NAFLD, and few guidelines for related conditions (e.g. diabetes, obesity) mention NAFLD or NASH.
37. Modification of lifestyle risk factors is the cornerstone of treatment for all NAFLD patients, regardless of disease stage. This generally focuses on two goals: (1) reduction in body mass index (BMI); and (2) increasing levels of physical activity. These measures are equally important for other cardiometabolic conditions, highlighting the need for coordination approaches to addressing these risk factors.
38. Lifestyle changes are however challenging to implement and sustain over the long term.
39. The lack of pharmacological treatment is a challenge, particularly for patients with advanced disease.
40. Self-assessment and management tools have proven invaluable and empowering for patients at risk for other chronic disease conditions during the COVID-19 pandemic. This is an area that is yet to be explored widely for NAFLD.

- Cross-discipline collaboration would be greatly facilitated by multidisciplinary clinical guidelines and more evidence on the effectiveness of different multidisciplinary care models. Screening recommendations should be incorporated in clinical guidance for various comorbidities.
- Action is needed to raise awareness and implement proven measures in high-risk groups. More evidence on the impact of different screening and active case finding approaches will support this.
- NAFLD should be integrated into multimorbidity chronic disease management, which is usually handled in primary care. By integrating it within this framework the additional burden placed on GPs can be minimised while also promoting continuity of care of affected individuals. Long-term cost effectiveness data will help to convince payers and other stakeholders about the benefits of this approach.
- Finding enthusiastic clinicians to serve as NAFLD champions could be instrumental in fine-tuning new approaches to care and making them standard practice.
- Evidence of better outcomes will help obtain buy-in for expanding proven approaches. Operational research is needed to study the development and implementation of pathways and care model.

Developing and regulating therapies and financing care

41. Developing effective pharmacological treatments and demonstrating that benefits outweigh risks will be particularly challenging for NAFLD because it is a slowly progressing multifactorial disease.
42. There has been major progress in harmonizing the approval and regulatory processes for pharmacological treatments across countries and regions.
43. Implementation and cost–effectiveness research will be critical, both to find the most effective ways to put new therapeutics and models of care into practice, but also to persuade payers to reimburse for these.

- Implementation research funding will need to come from a variety of sources, ranging from global and national public health agencies and philanthropic organisations to the private sector.
- It may be fruitful to form an international coalition of funders who are willing to provide catalytic funding to support these efforts.
- The case for research will need to be developed and promoted by a wide group of stakeholders, including national associations and leading experts. The EILF – Wilton Park dialogue series will also help to facilitate this.

The patient community

44. People living with NAFLD often feel confused and isolated when they receive a diagnosis, as a patient informed the participants during this dialogue.
45. Following a diagnosis, patients often only receive general advice around exercising more and eating healthier, with little change in the management strategies.
46. There is broad agreement on the critical importance of developing NAFLD patient communities as soon as possible – but acknowledgment of the difficulties in doing so.

47. Building such communities for NAFLD will be tremendously challenging because patient symptoms are linked chiefly to other comorbidities. Moreover, there is currently no NAFLD policy agenda for potential patient advocates to be inspired by or to act upon.

48. There is widespread support for connecting with patient advocacy groups for other NCDs, especially obesity and diabetes, and helping them to develop NAFLD subgroups. One thing these subgroups could focus on would be incorporating NAFLD into the relevant clinical guidelines and information materials for their disease areas.

49. The NCD Alliance, which has a global network of over 2,000 organisations in 170 countries, may offer good opportunities for networking, partnership, advocacy and capacity development, especially for NAFLD patient groups.

- NAFLD policies and care models should be patient-centred. This will require the engagement of patients and patient organisations throughout the design and delivery process. Patient advocates should be identified, recruited and trained. Advocates from different geographical areas can also be convened to share lessons and experiences
- Patient stories should be promoted to give NAFLD a human face, thereby increasing awareness and support among policymakers, healthcare professionals and the general population.
- Physicians and nurses should be encouraged to facilitate contacts among NAFLD patients; digital platforms like Facebook, LinkedIn and Twitter could be used to establish such groups.

Policy strategies for addressing NAFLD

50. No country in the world has a national strategy or action plan for NAFLD. NAFLD is also not mentioned in other key strategies, such as those addressing diabetes or NCDs more broadly.

51. Non-communicable diseases, and especially obesity, are often seen as the result of personal lifestyle choices, however, individual choice is significantly constrained by environmental and societal factors.

52. As with obesity and diabetes, preventing and treating NAFLD is primarily a societal responsibility, rather than an individual one, and will require a systems approach, with strong leadership to address both the direct and underlying causes of disease at the social, economic and political level.[4]

53. Collaborative efforts between sectors and disciplines, from health and food to education and urban planning are needed to tackle the major risk factor associated with NCDs. For NAFLD, the major targets are poor diets and physical inactivity.

54. There is also overlap between risk factors for NAFLD and alcohol-related liver disease (ARLD). The two diseases can coexist and EASL recommends treating them and preventing them simultaneously.

55. Financial mechanisms, such as taxation and the subsidizing of healthy foods, and legislation, including on the marketing of unhealthy products and nutritional labeling, are some of the policy options available to governments. Mandatory front-of-package labeling for unhealthy foods is one tool to drive manufacturers to reformulate their products to be healthier.

[4] https://www.nature.com/articles/s41575-020-0315-7

56. Countries can implement a corresponding series of policy actions to encourage physical activity, from urban design and access to green spaces, to re-pedestrianizing cities.

57. Efforts in many of these areas are ongoing and being led by organizations and individuals in other sectors. The liver health community should seek to engage with those leading these efforts. Initiatives, such as the 2021 UN Food Systems Summit, provide an opportunity for the liver community to add their voice to ongoing calls to transform food systems to deliver healthy diets.

58. The Sustainable Development Goals (SDG), which consist of 17 goals and 169 targets, provide a blueprint for multisectoral action on global development. The SDGs can provide a useful framework for thinking about the cross-sectoral actions that can make a difference in addressing NAFLD. This goes beyond the health specific goal (SDG 3) and NCD target (SDG 3.4) with many other SDGs providing entry points for responding to NAFLD.

- In preparing the NAFLD public health roadmap, existing policy efforts in the NCD space should be mapped to identify where the NAFLD community can engage in these efforts (e.g. on food systems and healthy eating).
- In certain areas the liver health community can take the lead, such as championing access to proven primary care interventions that support individuals to address chronic disease risk factors.
- Simple ways to communicate the NAFLD public health agenda are needed. One effective way would be to develop a memorable acronym, akin to the ROOTS framework for obesity and MPOWER for tobacco policies.
- A small number of policy priorities should be identified and championed by those working on NAFLD. Careful consideration of how to communicate these priorities will be needed, following the head, heart and pocket analogy.
- A multisectoral framework for action is needed. This can be inspired by previous work on obesity and should include a diagram that helps to communicate the relationship between NAFLD and various sectors. The Sustainable Development Goals provide a useful starting point for this.

Developing a public health roadmap for NAFLD: next steps

59. EILF is leading the process of developing a global public health consensus statement for NAFLD. The consensus statement, which will include input from over 200 experts, will outline the current thinking in the field and establish priority actions to move this agenda forward. The findings will be published in late 2021.

60. In parallel, EILF and others are working to develop a roadmap that will help to operationalize the recommendations. The roadmap will be a strategic document that outlines how the priority actions can be put into practice, the stakeholders that need to be involved in this process and how progress can be monitored.

61. A global coalition of individuals and organizations will steward and coordinate this process. The coalition will engage champions, trailblazers and high-profile individuals from across disciplines and sectors to help build momentum around this cause.

62. As these efforts advance, focus will be placed on involving those working outside of liver health by engaging at the edges of the coalition’s network in order to grow and achieve a critical mass.

63. In the second half of 2021, EILF and Wilton Park will convene stakeholders for the second dialogue in the series.

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This report was written by Misha Hoekstra, Henry Mark & Jeffrey Lazarus

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