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Integrating Polygenic Risk Scores and Proteomics: A New Paradigm for Predicting Health Risks

Introduction

Revolutionizing Disease Prediction via the Convergence of Genetics and Proteomics

Advances in Genomics Technologies: Progress over the past two decades has improved our understanding of genetic risk architecture and facilitated the development of polygenic risk scores (PRS) to help predict disease risk based on multiple gene variants.

Advances in Proteomics Technologies: In the last five years, there have been substantial improvements in these technologies. These advancements have increased the precision and scalability of protein analysis, enabling tools like liquid biopsy. This allows for major population health studies and better disease risk predictions by identifying actionable biomarkers and providing new insights into biological pathways.

Significance for the Scientific Community: There is a widespread optimism that protein biomarkers will help bridge the genotype-phenotype gap. This could lead to the creation of new clinical tools and hasten the development of precision medicine.

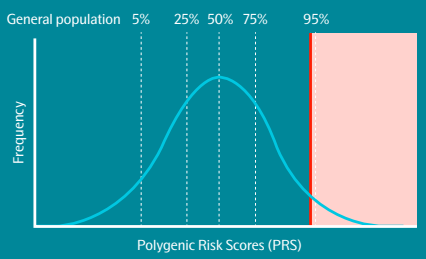
Focus of the White Paper: This white paper examines the dual approaches of polygenic risk scores and proteomic profiling. Together, these technologies are setting new standards in the early detection and prevention of diseases, promising a new era in personalized medicine through their integration.

Decoding Polygenic Risk Scores: The Genetic Blueprint of Disease Prediction

Polygenic risk scoring (PRS) is a genetic approach that evaluates an individual's risk of developing a particular disease based on multiple genetic variants across the genome. Developed from genome-wide association studies (GWAS), PRS aggregate the effects of numerous genetic variants, providing a nuanced risk assessment tool. One of the key advantages of PRS is their ability to capture the cumulative effect of numerous genetic variants, each with a small contribution to disease risk. PRS represent a quantum leap in our ability to gauge an individual's predisposition to various diseases.

Polygenic risk scoring (PRS) is a genetic approach, developed from genome-wide association studies (GWAS), that evaluates an individual's risk of developing a particular disease based on multiple genetic variants across the genome.

PRS have sparked considerable interest in healthcare circles, promising a revolutionary shift in disease prediction and stratification. With over 2,500 diseases or traits under scrutiny, PRS have garnered attention for their potential ability to enable more personalized approaches to those in different areas of the risk portfolio. Indeed, commercial genetic testing services and pilot trials within healthcare systems reflect a growing interest in the application of PRS. Despite their promise, PRS face ethical and scientific challenges, notably a bias towards populations of European descent, which may limit their utility across diverse populations (Martin et al., 2019). Their biased predictive power is attributed to the overrepresentation of European individuals in genetic studies, and their use could inadvertently worsen health disparities. Martin et al. (2019) recommend increasing the diversity in genetic studies and making summary statistics publicly available as crucial steps towards reducing disparities in the utility of PRS.



Recent studies have explored the role of PRS in enhancing predictions for diseases such as coronary heart disease (CHD) and breast cancer. While the studies demonstrated a significant correlation between PRS and CHD risk, the incremental improvements over traditional risk factors have been modest. For instance, a review involving over 45,000 single-nucleotide variations found limited enhancement in clinical decision-making when PRS were added to existing risk assessment models (Groenendyk et al., 2022)

Further analysis (Hingorani et al., 2023), underscores the need for a nuanced evaluation of PRS. This study, which utilized data from the Polygenic Score Catalog, revealed that while PRS could distinguish risk at a statistical level, the practical benefits for clinical application might require re-evaluation, particularly in primary prevention settings.

Integrating PRS with traditional risk models and proteomic insights offers a promising avenue to deepen our understanding of disease mechanisms. Proteomic technologies, by measuring protein biomarkers, contribute significantly to refining these predictions and could potentially close gaps left by genetic-only approaches. This integrated perspective not only enhances our understanding of genetic risk factors but also underscores the potential of proteomics in advancing precision medicine.

Proteomic technologies, by measuring protein biomarkers, close the gaps from genotype to phenotype.

Proteomics Breakthroughs: Refining Disease Risk with Protein Biomarkers

Recent advances in proteomics have greatly enhanced our capacity to analyze protein biomarkers with unprecedented precision and scale. Techniques such as liquid biopsies have facilitated major population health studies, offering profound insights into biomarkers and biological pathways that underpin diseases. This segment examines how proteomics, through detailed protein profiles, is bridging the genotype-phenotype gap and heralding new clinical tools for precision medicine.

The work by You et al. (2023) explores the potential of blood proteomics in predicting the risk of multiple diseases and mortalities. The original clinical data for this study came from The UK Biobank Pharma Proteomics Project (UKB-PPP) which is the largest population-scale proteogenomic study undertaken to date. By leveraging the power of the Olink® Explore platform on more than 54,000 UK Biobank (UKB) participant samples, 14,000 genetic associations with protein expression levels were identified (81% of reported as novel) and discovered 3,000 biomakers of disease, across all major biological patheays. The full data has been released as an open access resource also freely available on Olink Insight.

UKB-PPP & Olink Explore
13 biopharmaceutical companies
54,000 UKB participant samples
14,000 genetic associations with protein expression levels
3,000 biomarkers covering all major biological pathways

You et al. (2023) introduced the concept of Proteomic Risk Score (ProRS), derived from plasma protein measurements for a wide range of conditions, including infectious, circulatory, respiratory, and digestive diseases, as well as various cancers and mortality. ProRS serves as an assay, offering a streamlined approach to assessing multi-disease risk. Their findings revealed important insights into the predictive power of ProRS. Individuals with higher ProRS percentiles showed elevated risks across all disease categories and mortality, as depicted by distinct Kaplan-Meier survival curves. Specifically, those in the top ProRS tertile exhibited significantly higher risks of all-cause mortality and specific diseases compared to those in the bottom tertile. Remarkably, certain proteins, such as GDF15, CDCP1, CXCL17, EDA2R, and HAVCR1, emerged as critical predictors across multiple disease categories, suggesting shared underlying pathways among different diseases.

The study also assessed the clinical utility of ProRS, demonstrating its reliability and reproducibility in clinical practice. ProRS generally outperformed established clinical predictors for most investigated endpoints. Even when combined with clinical predictors, ProRS showed significant enhancements in predictive capability, highlighting the potential of blood proteomics in improving risk stratification. By uncovering shared predictive proteins and demonstrating the superiority of ProRS over traditional clinical predictors, this research opens new avenues for disease prevention, personalized medicine, and targeted interventions. These findings sustain the promising potential of blood proteomics as a powerful tool for informing multi-disease risk prediction and guiding clinical decision-making.

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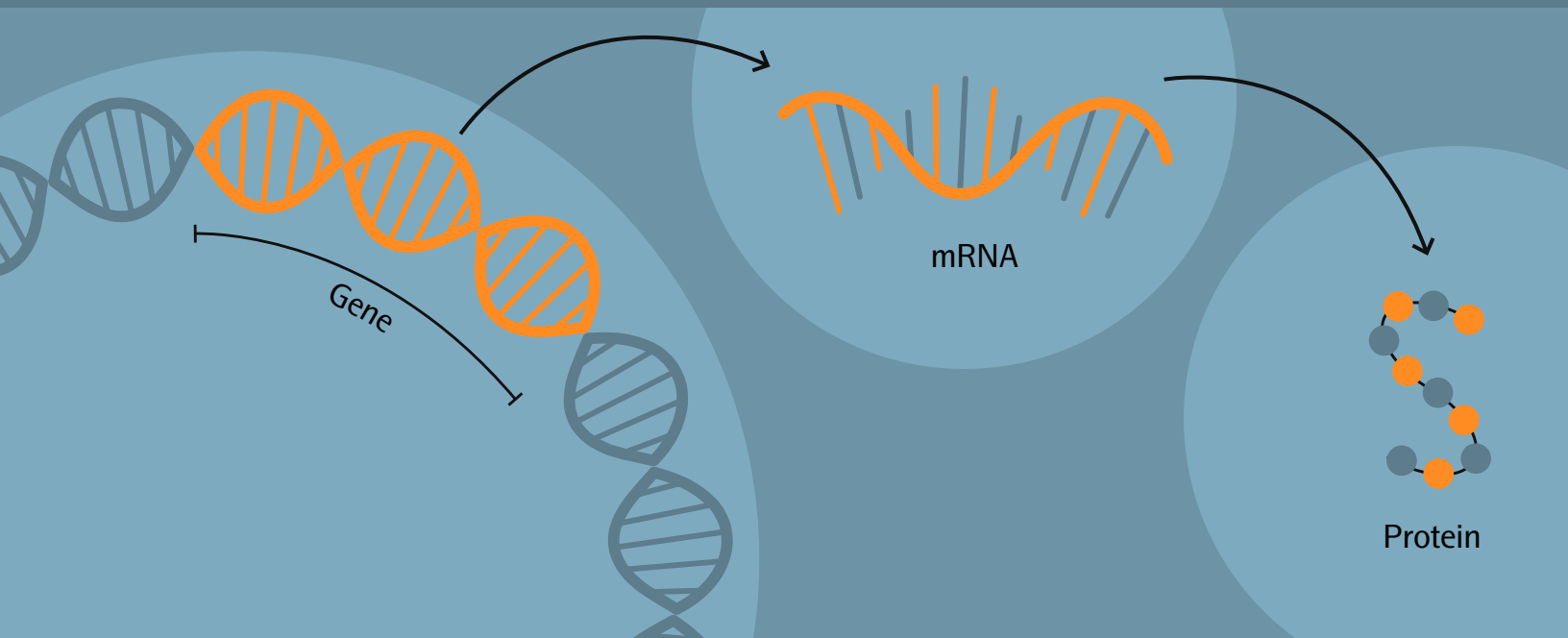
Genes *vs.* Proteins: A Comparative Analysis of Disease Prediction Technologies

Comparing the efficacy of PRS and proteomic risk scoring unveils their distinct yet complementary roles in medical research. While PRS provides a broad genetic outlook on disease predisposition, proteomic profiling offers a dynamic view of disease progression and response to treatment. This section presents a critical appraisal of both methodologies, based on peer-reviewed articles and recent studies, illustrating their individual strengths and potential synergies.

Proteomic profiling offers a dynamic view of disease progression and response to treatment.

In a recent publication, Møller et al. (2023) investigated the complementary roles of PRS and proteomics in ruling out diagnosis of coronary artery disease (CAD) in patients presenting with new-onset chest pain. By integrating PRS and targeted proteomics with clinical risk factors, the researchers achieved a significantly higher predictive accuracy for ruling out CAD compared to using traditional clinical models alone. Specifically, the combination of the genetic and proteomic markers with the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) minimal risk score (PMRS) improved the area under the curve (AUC) for predicting CAD absence from 0.76 to 0.80. This enhancement underscores that PRS and proteomic data integrated with clinical risk assessments yields a more robust and comprehensive diagnostic tool.

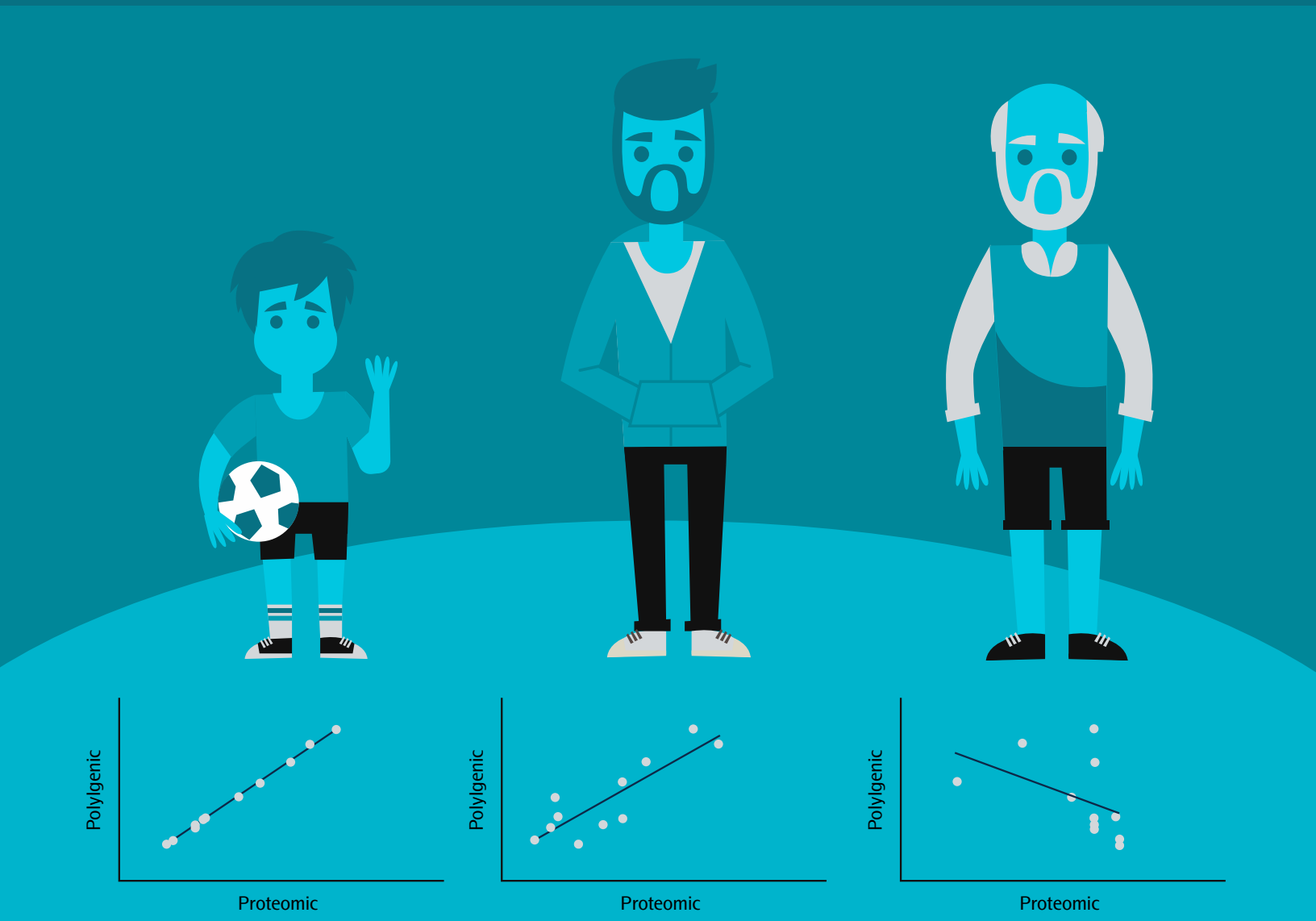
As we advance our understanding of disease prediction through genetic and proteomic markers, it is crucial to address the intricate dynamics between PRS and proteomics, particularly in the context of aging. Research reveals a nuanced relationship where PRS, which predict the risk of age-related diseases such as Alzheimer's disease (AD), display a negative correlation with proteomic biomarkers due to epigenetic influences (Li et al., 2020). For example, individuals with a higher PRS for AD often show lower levels of amyloid-beta peptides in cerebrospinal fluid (CSF), which contrasts with the elevated levels typically observed in AD patients. This inverse correlation suggests that genetic predispositions captured by PRS can lead to alterations in protein expressions or biomarker levels through mechanisms that are not solely genetic.



Complex Interplay of PRS and Proteomics in Aging: The Role of Epigenetics

Epigenetic modifications, including DNA methylation and histone changes, are pivotal in mediating the interaction between genetic risks and protein expressions. These modifications can suppress or enhance the expression of genes associated with disease risks, thereby influencing the correlation between PRS and proteomic outcomes. For instance, altered methylation patterns have been linked to changes in gene in the brain vasculature associated with AD risk, potentially modulating the disease's biomarker profiles contrary to what might be expected based solely on genetic risk (Oh et al., 2023).

The epigenetic modulation of gene expression presents both challenges and opportunities in disease prediction and management. For older adults, the negative correlation between PRS and proteomic biomarkers might suggest a delayed onset or altered pathophysiology of diseases like AD. However, this correlation can also be influenced by other factors such as lifestyle, environmental exposures, and other genetic variations. This complexity necessitates a more integrated approach in risk assessment models that consider genetic, proteomic, and epigenetic data to accurately predict and manage age-related diseases.



Case Studies in Polygenic and Proteomic Risk Assessment

Real-world applications of PRS and proteomics vividly demonstrate their impact on healthcare. This section includes summaries of landmark studies that illustrate how these technologies are used in diagnosing and predicting diseases such as coronary artery disease, dementia, and various cancers. Notably, the integration of PRS with proteomic data and clinical risk factors has shown significant promise in enhancing diagnostic accuracy and patient outcomes.

In their work, Guo at al. (2024) examined data from 52,645 adults without dementia at enrollment in the UKB, with 1,417 incident cases and a follow-up time of 14.1 years. Among 1,463 proteins measured in plasma, GFAP, NEFL, GDF15 and LTBP2 consistently associated with the incidence of all-cause dementia (ACD), AD, and vascular dementia (VaD), ranking high in protein importance ordering. The predictive power of these proteins was further enhanced when combined with demographic data. GFAP and GDF15 produced highly desirable predictions for ACD, proving effective even when predicting outcomes over a span of 10 years. The study revealed that individuals with higher GFAP levels were 2.32 times more likely to develop dementia. Remarkably, both GFAP and NEFL began to show changes at least 10 years before the clinical diagnosis of dementia, highlighting their potential as early indicators of the disease. The findings strongly highlight GFAP as an optimal biomarker for dementia prediction, with implications for screening people at high risk for dementia and for early intervention. The identification of protein signatures marks a significant advancement in dementia research. These biomarkers not only facilitate early detection but also enable more precise risk stratification and tailored preventive measures, potentially transforming how we approach dementia risk management. Apart from the obvious implications and impact in the dementia clinical settings, the work from Guo et al. (2024) is an important proof of protein biomarkers' significance in disease risk assessments.

In another study based on a remarkable interrogation of the UKB-PPP dataset, Papier et al. (2024) identified multiple proteomic risk factors for 19 different cancers. Around 1,500 proteins were measured using the Olink® Explore platform in more than 44,000 UKB participants, ~10% of whom developed some form of cancer over a median follow-up period of 12 years. This observational prospective analysis revealed 618 associations between protein levels and 19 different cancers. This corresponded to 371 different proteins, of which 107 retained significance at more than 7 years prior to diagnosis. Almost 40 of these proteins are the targets of approved drugs, with the majority for non-cancer indications, suggesting potential repurposing opportunities towards oncology. Supporting genetic evidence also provided indications that 29 proteins may have causal roles in cancer development. These important findings present opportunities for early diagnosis and potential repurposing of existing drugs towards oncology, emphasizing the role of proteomics in cancer prevention and treatment. The authors concluded that "We discovered multiple associations between blood proteins and cancer risk. Many of these were detectable more than seven years before cancer diagnosis and had concordant evidence from genetic analyses, suggesting they may have a role in cancer development. We also identified proteins that may mark early cancer processes among carriers of established cancer risk variants, which may serve as potential biomarkers for risk stratification and early diagnosis".

One final example of the enhanced power of the protein signatures can be found in the publication from Carrasco-Zanini et al (2024) where the authors describe their work as follow: "Our study takes a comprehensive approach, integrating proteomic data, genomic data, and data from electronic health records to systematically derive sparse protein signatures for prediction across 23 diverse incident diseases and all-cause mortality. Our results show that as few as five proteins outperformed polygenic risk scores for the majority of outcomes, and improved the prediction of seven outcomes over common risk factors. We further developed a sparse multimorbidity signature of ten proteins, which improved the prediction of individual diseases over common risk factors."

Future Development and Clinical Impacts of Integrated Risk Scores

As we look beyond the current state of disease prediction, the integration of PRS and proteomic technologies heralds a transformative shift in precision medicine. While PRS alone has shown limited utility in enhancing clinical decision-making, their combination with proteomic profiles promises a more comprehensive understanding of disease mechanisms. Future pathways will likely focus on leveraging these integrated risk scores to refine diagnostics, tailor preventative strategies, and enhance therapeutic interventions. The potential clinical impacts are vast, ranging from improving risk stratification to enabling earlier and more personalized treatments.

As research continues to evolve, it is essential to ensure these technologies are accessible and equitable, allowing benefits to be universally shared. This integrative approach will not only push the boundaries of current medical practices but also pave the way for a new era in healthcare, where precision and personalization take precedence. Further research is essential to deepen our understanding of how epigenetic mechanisms influence the relationship between genetic predispositions and proteomic changes in the aging population. Unraveling these connections will enhance our ability to develop targeted interventions and personalized management strategies that effectively address the multifaceted nature of age-related diseases.

Envisioning the Future of Personalized Medicine: Implications of Integrated Genetic and Proteomic Approaches

The convergence of polygenic and proteomic technologies is not merely an incremental advance in medical science, but a paradigm shift towards truly personalized medicine. By providing a more complete picture of an individual's health risks and tailoring interventions accordingly, these technologies are poised to dramatically improve health outcomes. The identification of key protein biomarkers not only facilitates early detection but also enhances the precision of risk stratification and the development of tailored preventive measures.

As the field of proteomics continues to evolve, it holds the promise of revolutionizing our approach to disease prediction, prevention, and personalized healthcare, offering new hope for better health outcomes across a range of diseases. This evolving landscape also underscores the importance of integrating diverse biological data streams, including PRS, proteomics, and epigenetics, to forge a comprehensive framework for predicting and combating diseases in an aging society. Such integrative approaches will not only refine our predictive models but also pave the way for innovations in therapeutic strategies that are attuned to the complexities of human biology.

The convergence of polygenic and proteomic technologies is a paradigm shift towards truly personalized medicine.

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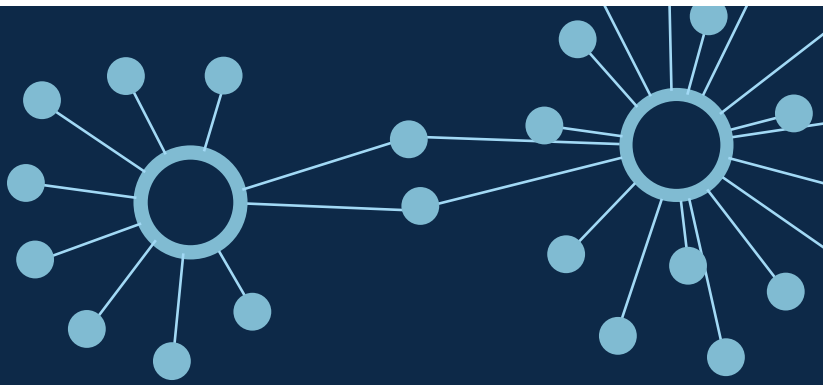

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