

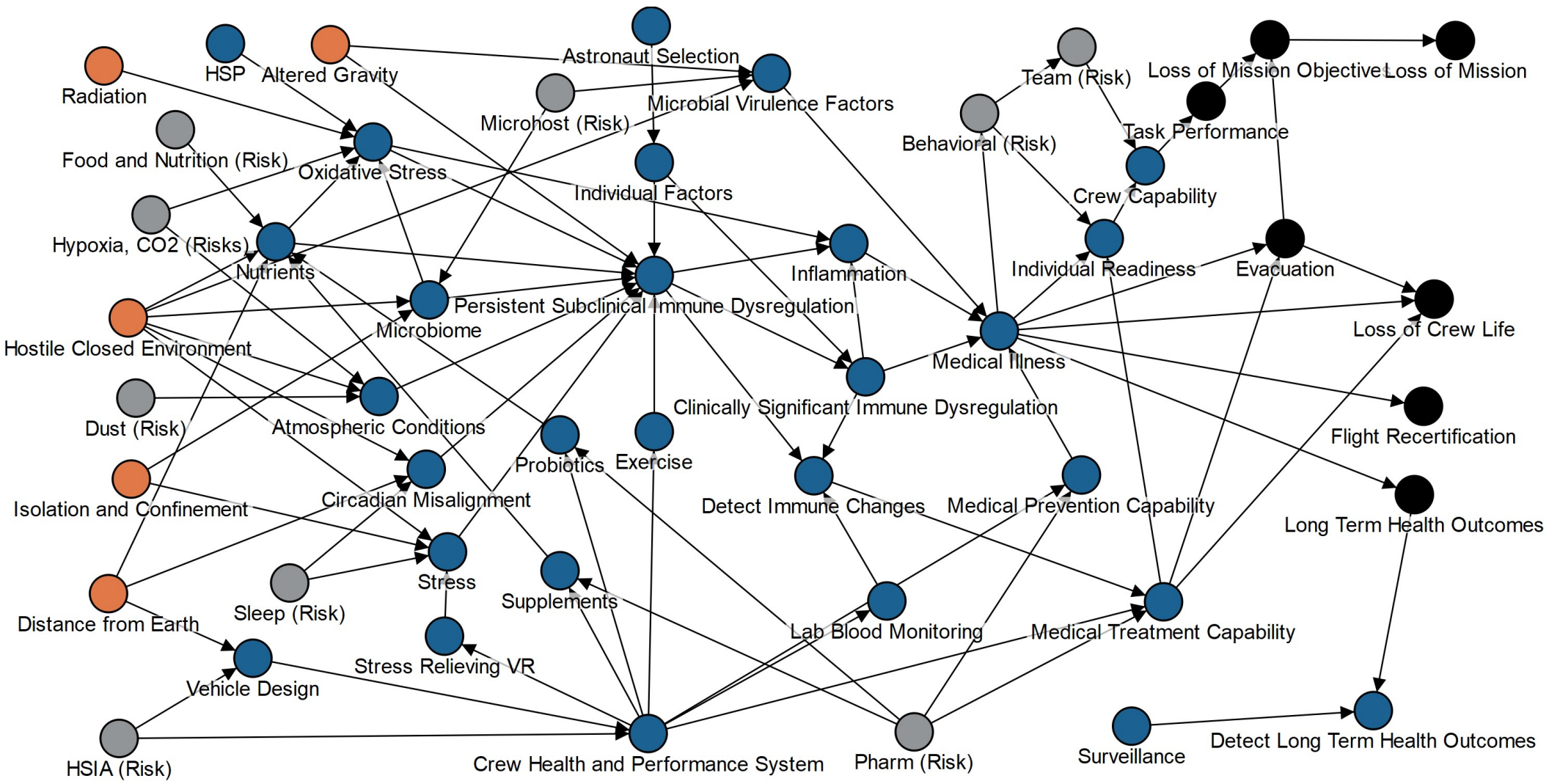
This Directed Acyclic Graph and write-up is an excerpt from a larger NASA document.

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**Directed Acyclic Graphs: A Tool for Understanding the NASA
Spaceflight Human System Risks**

Human System Risk Board

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Immune Risk DAG Narrative

The central issue in the Immune Risk is the progression from Persistent Subclinical Immune Dysregulation -> Clinically Significant Immune Dysregulation -> Medical Illness. Oxidative Stress, Persistent Subclinical Immune Dysregulation and Clinically Significant Immune Dysregulation can affect Inflammation levels in the body that contribute to Medical Illness.

- **Subclinical Immune Dysregulation** refers to changes in cellular proliferation and function that does not have a known clinical issue directly following it.
- **Clinically Significant Immune Dysregulation** refers to the threshold at which those cellular issues have a known prognostic indication for impending disease.
- The **Medical Illnesses** that can result are a function of both hypoactive and hyperactive immune dysregulation.
- Hypoactive dysregulation predisposes astronauts to increased probability of infections.
- Hyperactive dysregulation predisposes astronauts to increased probably of hypersensitivity reactions like rashes and autoimmune disease.

Increasing probability of **Medical Illnesses** contributes to deterioration of **Individual Readiness** and **Crew Capability** which affects **Task Performance**, likelihood of **Evacuation** for medical reasons, and in severe cases can contribute to **Loss of Crew Life**. Persistent medical issues post flight and post career may affect **Flight Recertification** and **Long Term Health Outcomes**.

- Contributors to the start of this chain of events include:
- **Radiation** exposure leads to **Oxidative Stress** that can contribute to immune dysregulation.
- **Nutrients** which are dependent on safe and acceptable **Food and Nutrition (Risk)**.
- The **Microbiome** which is dependent on the status of the **Microhost (Risk)**.
- **Atmospheric Conditions** including airborne content affected by the **Hypoxia, CO2, Dust (Risks)**.
- **Circadian Misalignment** associated with the **Sleep (Risk)** is known to affect immune function.
- **Stress** associated with the **Behavioral (Risk)** is known to affect immune function.

Countermeasures that affect immune system function must be included in the **Crew Health and Performance System** and accommodated in **Vehicle Design**. These are affected by the **HSIA (Risk)** and include:

- Countermeasures that may prevent Persistent Subclinical Immune Dysregulation.
- **Probiotics** and **Supplements** which are dependent on the **Pharm (Risk)** and may require different storage modalities.
- Other stress relieving techniques such as **Stress Relieving Virtual Reality (VR)**.
- **Exercise** has been shown to improve Subclinical changes in the immune system.
- **Lab Blood Monitoring** enables the ability to **Detect Immune Changes** that are either subclinical or clinically significant. When detected, these can enable further interventions including:
 - **Medical Prevention Capability** such as evaluations by the crew medical officer that can help reduce the causes of immune dysfunction.

- **Medical Treatment Capability** that responds to the infections or hypersensitivity reactions that occur and seek to minimize the consequences of those medical conditions.
- Both of these are dependent on the **Pharm (Risk)** as medications used are subject to stability and pharmacokinetic (PK)/pharmacodynamic (PD) issues.
- The likelihood of infectious diseases (**Medical Illness**) in a mission is also affected by **Microbial Virulence Factors** which have been shown to change in spaceflight.
- **Long Term Health Outcomes** that may occur as a result of immune dysregulation must be included in **Surveillance** post flight and post-career in order to effectively **Detect Long Term Health Outcomes** and characterize the magnitude of this risk in the Long Term Health domain. These can include hypersensitivity conditions, autoimmune disorders, and cancers.