

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

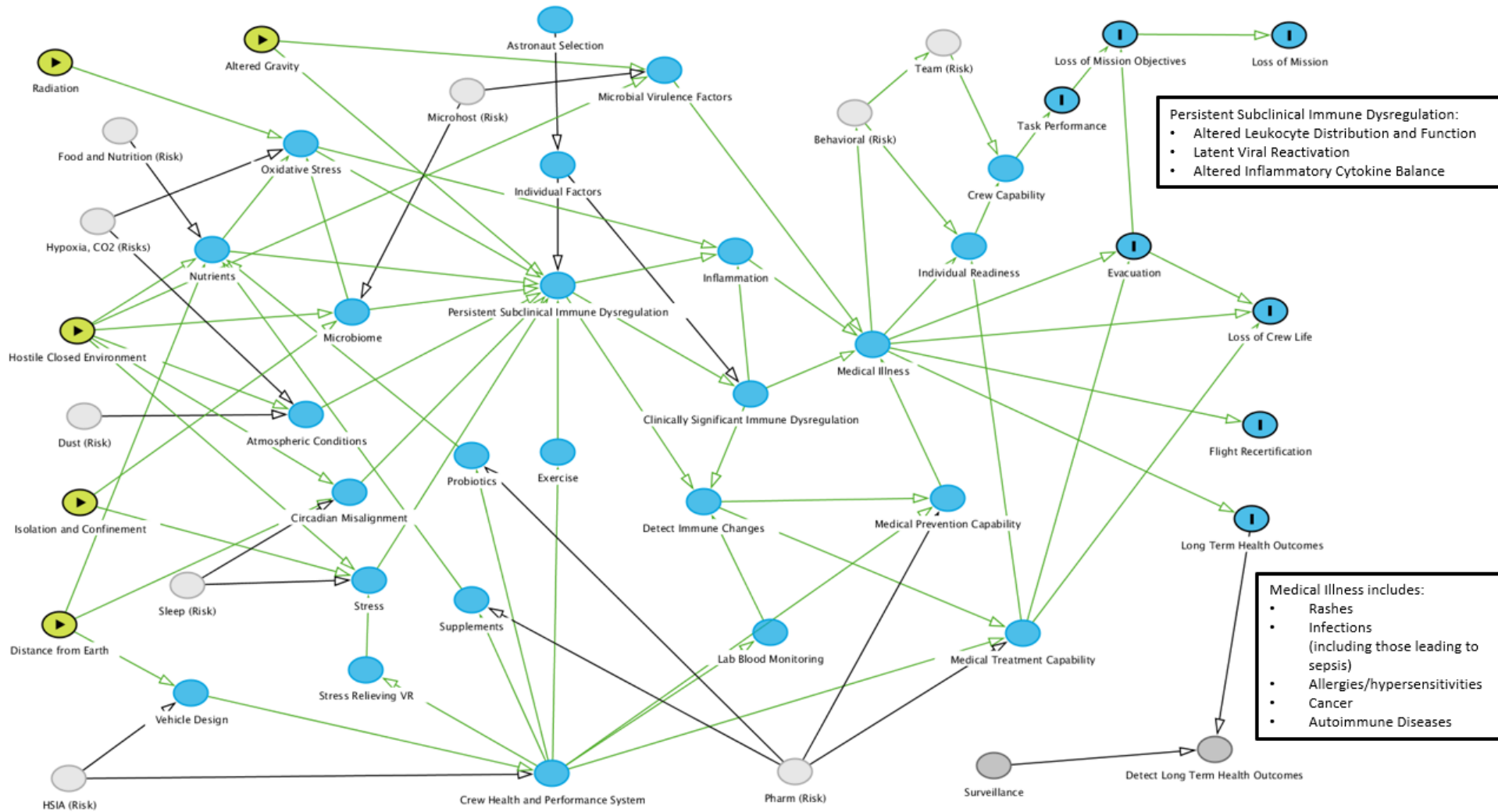
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**Directed Acyclic Graphs: A Tool for Understanding the NASA
Spaceflight Human System Risks**

Human System Risk Board

October 2022

Risk of Adverse Health Event Due To Altered Immune Response (Immune Risk)



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.