ASPEN 2025 NUTRITION SCIENCE & PRACTICE CONFERENCE

The Next 50 Years – Challenges and Opportunities in Clinical Nutrition

"Thinking Outside the Box"

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Disclosures

- No commercial relationships to disclose

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Learning Objectives

Upon completion of this educational activity, the learner will be able to:

- Gain understanding of fundamental innovation skills.
- Identify at least two significant breakthroughs in nutrition that resulted from thinking outside the box.
- Describe some of the key challenges and opportunities that we face in clinical nutrition.

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Definitions

- What is “thinking outside the box”?
  - An idiom that means to explore ideas that are creative and unusual and that are not limited or controlled by rules or tradition (Merriam-Webster).
- What is innovation?
  - Developing new insights, applying novel solutions to make improvements, encouraging creative thinking, exploring new ideas and methodologies, and taking calculated risks to integrate ideas in unique ways to advance research (NIH).
  - In the context of clinical nutrition, innovation would focus on the promotion of human health through the **prevention** and **treatment** of malnutrition and/or disease. In this construct malnutrition would also encompass undernutrition manifest as nutrient deficiencies in the settings of obesity, malabsorption, and other conditions.

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Introduction – "Thinking Outside the Box"

- Highlight the strategic importance of thinking outside of the box as we contemplate future directions and priorities in clinical nutrition.
- Emphasize the necessity of challenging dogma and asking questions when things do not make sense.
- Innovation skills prioritize new ways of looking at difficult problems and bringing new perspectives and creative solutions.
- Share approaches that are integral to successful innovation.
- Demonstrate the potential rewards and risks of thinking outside the box.
- Conclude by exploring some of the key challenges and opportunities that we face going forward.

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An illustrative vignette, Helicobacter pylori

- **Robin Warren and Barry Marshall** – Received the **2005 Nobel Prize**. https://www.nobelprize.org/prizes/medicine/2005/press-release/ Accessed Feb. 5, 2025.
- Isolated H. pylori in active chronic gastritis in 1982. First abstract and early papers were rejected.
- Infection elicits humoral and cell-mediated immune response that causes inflammation in gastric mucosa.
- Chronic superficial gastritis → atrophic gastritis → intestinal metaplasia → dysplasia.
- Fewer than 5% of carriers develop malignancy many years later. Cancer risk determined by H. pylori virulence factors and host polymorphisms that govern inflammatory response.
- Majority of gastric cancers worldwide are directly attributable to H. pylori.
- Colonization near universal in developing world. Acquired in childhood.
- With preventive and treatment measures the prevalence of gastric cancer has declined, but there remains appreciable global variability.

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Barry Marshall – Nobel Laureate

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Interview with Barry Marshall

- "I had been arguing with the skeptics for two years and had no animal model that could prove *H pylori* was a pathogen. If I was right, then anyone was susceptible to the bug and would develop gastritis and maybe an ulcer years later. So, I expected to develop an asymptomatic infection. The experiment was planned with a culture from a patient with dyspepsia and confirmation that it was sensitive to metronidazole. Then I underwent endoscopy in early July 1984 to confirm that I was negative for *H pylori*. Three weeks later, I drank the 'brew' which was a suspension of two culture plates of the organism. After five days, I started to have bloating and fullness after the evening meal, and my appetite decreased. My breath was bad and I vomited clear watery liquid, without acid, each morning. Then, a follow-up endoscopy showed severe active gastritis with polymorphonuclear infiltrate and epithelial damage. Gastritis was explained."

Marshall B, Adams PC. Helicobacter pylori: A Nobel pursuit. Can J Gastroenterol. 2008 Nov; 22(11): 895-896

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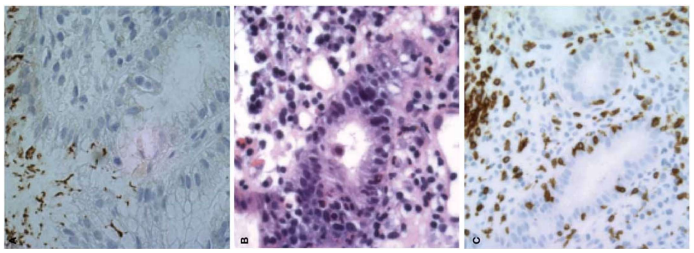
Gastric biopsy from a patient with chronic gastritis due to *H. pylori* persistence



Moss SF and Blaser MJ. Mechanisms of Disease: inflammation and the origins of cancer. Nat Clin Pract Oncol Nat Clin Pract Oncol 2005; 2:90–97.

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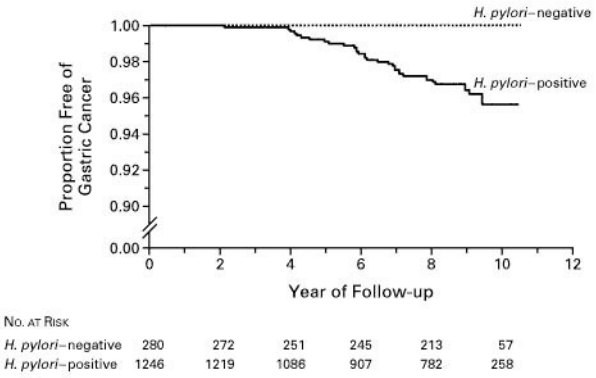
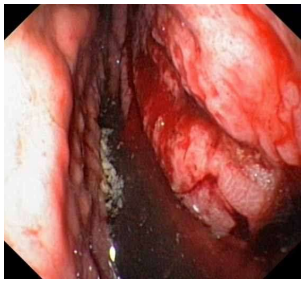
Kaplan-Meier Analysis of the Proportion of H. pylori-Positive and H. pylori-Negative Patients Who Remained Free of Gastric Cancer



The NEW ENGLAND JOURNAL of MEDICINE



Uemura N, et al. Helicobacter pylori infection and the development of gastric cancer. N Engl J Med 2001;345:784-789

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Treatment of scurvy: a classic innovation

- Thousands of British seamen were dying from scurvy, a disease caused by severe vitamin C deficiency. Manifestations included fatigue, bleeding gums, tooth loss, easy bruising, joint pain, poor wound healing, swollen legs, and ultimately death.
- In 1747, the Scottish surgeon James Lind, sailing on the HMS Salisbury, conducted what is acknowledged as the first randomized controlled clinical trial ever conducted.
- 12 sailors were assigned to treatment arms that included cider, dilute sulfuric acid, vinegar, seawater, plant extracts, or two oranges and one lemon daily. Those that received citrus improved.

Trohler U. Lind and scurvy: 1747-1795. J R Soc Med 2005;98:519-22.

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James Lind: the first clinical trial

- Full adoption by British navy took many years.
- British sailors came to be known as “limeys”.
- In 1928, Albert Szent-Györgyi isolated an adrenal substance, “hexuronic acid’”.
- In 1932, Charles Glen King isolated vitamin C and found that it was the same as 'hexuronic acid’.
- The chemical structure of vitamin C was determined by Norman Haworth in 1933 .

Carpenter KJ, The discovery of vitamin C. Ann Nutr Metab 2012; 61:259-264.

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Scurvy in modern clinical practice

- Life-threatening malnutrition in the setting of protracted substance use and compromised food intake.
- Presented with marked weight loss, poor dentition, anemia, edema, bruises, petechiae, and cork screw hairs.
- Carefully refed to avoid refeeding sequelae and given appropriate micronutrients.
- Scurvy responded to vitamin C replacement.

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Innovation - Total Parenteral Nutrition

- Dudrick, Wilmore, and Rhoads
- Landmark studies in dogs and then humans
- Faced skepticism and many challenges
- Protein hydrolysates / dextrose
- Lipid emulsions came later
- Enables many patients to survive who otherwise would have died.

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Major challenges to the development of TPN

- Formulate complete parenteral nutrient solutions (did not exist).
- Concentrate substrate components to 5-6 times isotonicity without precipitation (not easily done).
- Demonstrate utility and safety of long-term central venous catheterization (not looked upon with favor by the medical hierarchy). Received push back from mentors.
- Demonstrate efficacy and safety of long-term infusion of hypertonic nutrient solutions (contrary to clinical practices at the time).
- Maintain asepsis and antisepsis throughout solution preparation and delivery (required a major culture change).
- Anticipate, avoid, and correct metabolic imbalances or derangements.

Dudrick SJ. History of parenteral nutrition. J Am Coll Nutr 2009;28:243-51.

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Innovation - Folic Acid and Neural Tube Defects

- Landmark studies found that in women with a previous child with spina bifida, the use of high dose folic acid supplements markedly reduced the risk of having another child with a neural tube defect.
  - Smithells RW, Nevin NC, Seller MJ, et al. Further experience of vitamin supplementation for the prevention of neural tube defect recurrences. Lancet 1983;1:1027-31.
  - Smithells RW, Sheppard S, Wild J, Schorah CJ. Prevention of neural tube defect recurrences in Yorkshire: final report. Lancet 1989;2:498-9.

https://www.cdc.gov/birth-defects/about/neural-tube-defects.html Accessed February 6, 2025.

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Innovation - Folic Acid and Neural Tube Defects

- Godfrey Oaks (CDC) leveraged these findings to push for fortification of flour. There was strong resistance due to the possibility of masking underlying B12 deficiency, but in January 1998, fortification was mandated in the USA. Outcome studies in countries adopting mandatory fortification have revealed up to a 78% reduction in neural tube defects.
  - FDA US Food Drug Adm. Food standards: amendment of standards of identity for enriched grain products to require addition of folic acid; final rule. 61 Fed. Reg. 8781–97, March 5, 1996.
  - Crider KS, Qi YP, Yeung LF, et al. Folic acid and the prevention of birth defects: 30 years of opportunity and controversies. 2022;42:423-52.
- Heralded among the very top public health achievements.

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Innovation Skills

- **Associating** – synthesize novel inputs. Integrate from sources not usually entertained.
- **Questioning** – challenge status quo. Just because something has always been done one way does not mean that it is the best path.
- **Observing** – broadly to gain further insights. Look places that others may not have considered.
- **Networking** - collaborate and brainstorm in diverse interdisciplinary teams. Access new perspectives.
- **Experimenting** – test new hypotheses.

Adapted from Jeff Dyer, Hal B. Gregersen, and Clayton M. Christensen. The Innovator's DNA. Harvard Business Review. https://hbr.org/2009/12/the-innovators-dna Accessed February 5, 2025.

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Innovation Approaches

- Adapted from highly recommended book - Innovation Generation, Roberta Ness, Oxford University Press, New York, 2012.
- **PIG In MuD**
  - **Phrase** a question that is plausible and actionable.
  - **Identify** the paradigm and find alternatives. Examine analogies, broaden perspective, consider alternative choices and possibilities. Use group intelligence.
  - **Generate** solutions – use a team approach to brainstorming.
  - **Incubate** – pause and consider.
  - **Meld** best idea into science – test ideas, conduct experiments and clinical trials.
  - **Disseminate** – seek paradigm shift. Often encounter resistance, pushback, and bias. Need connected, knowledgeable, and convincing people. Find the right people and the right environment.

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The Next 50 Years: Research Challenges

Health systems research

- Can we fully integrate screening, assessment, intervention, and monitoring to promote improved outcomes for patients with disease-related malnutrition?
- Can we develop standardized approaches to diagnosis and data collection and reporting?
- Can we better train practitioners? There is need for a validated approach to diagnosis that incorporates key core variables that are amenable to use by practitioners with limited nutrition expertise or resources.
- Is there opportunity for a streamlined hybrid approach that integrates screening and assessment components for malnutrition diagnosis? In settings where feasible, this diagnosis should trigger comprehensive assessment and intervention.
- Appropriate and useful outcome measures are needed. Mortality, length of stay, complications, and readmission are complex multivariable outcomes that are impacted by many other variables besides nutritional status.

Jensen GL, Gramlich L. Malnutrition in disease and inflammatory states. In Modern Nutrition and Health and Disease. Eds. Tucker KL, Duggan CP, Jensen GL, Peterson KE, Ross AC, Touger-Decker R. Jones & Bartlett Publishing. 12th edition, 2025, pp. 1329-1336.

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The Next 50 Years: Research Challenges

Clinical/applied research

- Tailored population and disease specific interventions warrant further testing. There is a pressing need to identify those types of patients that are most likely to accrue benefits from such nutrition support, so that precision nutrition intervention will be possible.
- Technology development is needed to provide portable, valid, reliable, and inexpensive assessment of muscle mass and function that is applicable in diverse settings.

Basic research

- To support precision nutrition interventions, it will be necessary to identify and develop relevant biomarker panels, metabolic profiles, and genomic analyses. These advances will help to facilitate risk assessment, diagnosis, and monitoring of undernutrition and inflammation.
- Identify and test anti-inflammatory approaches, including dietary modifications and nutrient supplementation.

Jensen GL, Gramlich L. Malnutrition in disease and inflammatory states. In Modern Nutrition and Health and Disease. Eds. Tucker KL, Duggan CP, Jensen GL, Peterson KE, Ross AC, Touger-Decker R. Jones & Bartlett Publishing. 12th edition, 2025, pp. 1329-1336.

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The Next 50 Years: Challenges and Opportunities
Survey of nutrition thought leaders

- Charlene Compher
- Ainsley Malone
- Tommy Cederholm
- Al Barrocas
- Jeanette Hasse
- Peggi Gunter
- Isabel Correia
- Cristina Gonzales
- Heather Keller
- Marion Winkler
- Kris Mogensen
- Alison Steiber
- Leah Gramlich
- Ezra Steiger
- Terese Scollard
- Carol Ireton-Jones
- Juan Ochoa
- Vince Vanek
- John Hoffer
- Harriet Jager-Wittenaar

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Survey responses - challenges and opportunities - #1

- Build **large datasets** that capture **integrated** screening, assessment, interventions, and **relevant outcomes** to encompass inpatient, outpatient, and other settings across the continuum of care. These databases should be widely accessible. Sharing such data to enhance approaches to **care transitions** is a high priority.
- Use **artificial intelligence** with a machine learning approach to aid compilation, management, and robust analysis of complex data. There is clear potential for automated diagnosis using EHR data.
- **Support development of new laboratory panels and technologies** for malnutrition screening, diagnosis, and outcome monitoring. Ideally these would be well-validated, inexpensive, mobile, and readily accessible. For example, such approaches to body composition analysis are greatly needed.
- Development of sound approaches to malnutrition **screening and assessment in persons with obesity** warrants urgent attention.

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Survey responses - challenges and opportunities - #2

- Further development is indicated for **assessments of malnutrition, micronutrient status, muscle mass, and food intake.** Examples might include breath testing for metabolites, self-monitoring devices like high-tech garments, digital analysis of photographs of physical findings and of consumed food portions/plate waste, and development of rapid diet quality screening. Monitoring devices offer great potential to monitor safety and outcomes for nutrition support in the home and other non-acute care settings.
- Simple objective measures of **fitness** are needed. How can specific physical activity interventions be better integrated with nutrition care?
- Better understanding is needed of **metabolic changes** associated with inflammation. What is adaptive and what is pathologic? How can they best be modulated?
- Use metabolic and genetic profiling to deliver **precision nutrition care**. Be sure to also consider signals that reflect the pathophysiology of malnutrition. Precision care should include approaches to identifying those likely to benefit from specific interventions.

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Survey responses - challenges and opportunities - #3

- **Training** and **educational materials** (digital and written) should be translated and widely disseminated.
- **Social media** are powerful tools for broad community outreach. NGOs, food pantries, charitable agencies, and other such entities are also appropriate places for screening and outreach.
- Note that there is **disease-related malnutrition** and there is also **malnutrition-related disease**. The latter should not be overlooked. It is common for them to occur together.
- Prioritize development and testing of **consensus criteria** for **global diagnosis** of malnutrition. This approach aims to capture the minimum dataset for malnutrition diagnosis. These core criteria are essential to evaluate the success of interventions.

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Conclusions

- With the growth of AI - “In 50 years will physicians or dietitians ever have to see or touch a patient to diagnose and treat malnutrition or disease?” (Dr. Vanek)
- My sense is that the input of healthcare and nutrition providers will still be required for confirmation of diagnosis, implementation of interventions, and interpretation of outcomes.
- There are a host of concerns that have the potential to put much of what we do in clinical nutrition at risk like global and regional conflicts, global warming and extreme weather events, compromise of food and water supplies, our ability to sustain healthcare and nutrition care resources, our ability to support food assistance programs, our ability to support biomedical and nutrition research, and the potential appearance of new diseases and pandemics.
- There are also opportunities to address some of these concerns in the realm of ethics, policies, and law. What is technologically possible? What should be done ethically? What must be done legally?

Cardenas D, et al. Nutritional care is a human right: Translating principles into to clinical practice. Nutr. Clin. Pract. 2022;37:743–751.
Barracos A. 50 years later: Where have we been and where are we going? Nutr. Clin. Pract. 2025;40:10–15.

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Please think outside the box as we contemplate our future challenges and opportunities in clinical nutrition.

- Please reach out to share your ideas using the sticky Post-it note board at the ASPEN25 booth.
- It has been suggested on more than one occasion that I should go back in the box, but I have not let it dissuade me.☺
- Challenge dogma and ask questions when things do not make sense. If you have an idea, do not be afraid to share it.

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Key Priority

- Can we promote common global malnutrition terminology and characteristics for core criteria so that we can share meaningful data to evaluate prevalence, test targeted interventions, and monitor appropriate outcomes? **Yes, we can!**

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Learning Assessment Question #1

Identify two significant breakthroughs in nutrition that are in current use that resulted from thinking outside the box.

A. Total parenteral nutrition.

B. Folic acid supplementation to decrease risk for neural tube defects.

C. Complete transdermal nutrition that meets all nutritional requirements.

D. A single laboratory blood test that diagnoses malnutrition in any patient condition or setting.

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Learning Assessment Answer

Multiple choice question 1?

1. Options A and C (C is false)

2. Options B and C (C is false)

3. Correct answer options A and B – The development of total parenteral nutrition for intravenous feeding and folic acid fortification to decrease risk of neural tube defects are significant breakthroughs in nutrition that are in current use and resulted from thinking outside the box.

4. Options C and D (C and D are false)

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Learning Assessment Question #2

Robin Warren and Barry Marshall received the Nobel Prize for their pioneering research on which of the following?

A. Vitamin C deficiency

B. DNA structure

C. Gene editing

D. Helicobacter pylori

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Learning Assessment Answer

Multiple choice question 2?

1. Option A is false

2. Option B is false

3. Option C is false

4. Correct answer option D - Helicobacter pylori and its role in gastritis and peptic ulcer disease.

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Learning Assessment Question #3

What is the primary analysis concern with using outcomes like length of stay, complications, and mortality for hospital-based nutrition intervention studies?

A. These are very difficult outcomes to measure.

B. These are complex multi-variable outcomes.

C. It is not plausible that malnutrition is associated with these outcomes.

D. It is already well established that nutrition interventions favorably alter the course of individuals with advanced cancer cachexia.

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Learning Assessment Answer

Multiple choice question 3?

1. Option A is false

2. Option B is true - These are complex multi-variable outcomes of which nutrition is but one variable. This makes it very difficult to demonstrate the benefits of nutrition interventions using these outcomes.

3. Option C is false

4. Option D is false

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8. https://www.cdc.gov/birth-defects/about/neural-tube-defects.html Accessed February 6, 2025.

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