Trimethylaminuria (TMAU)

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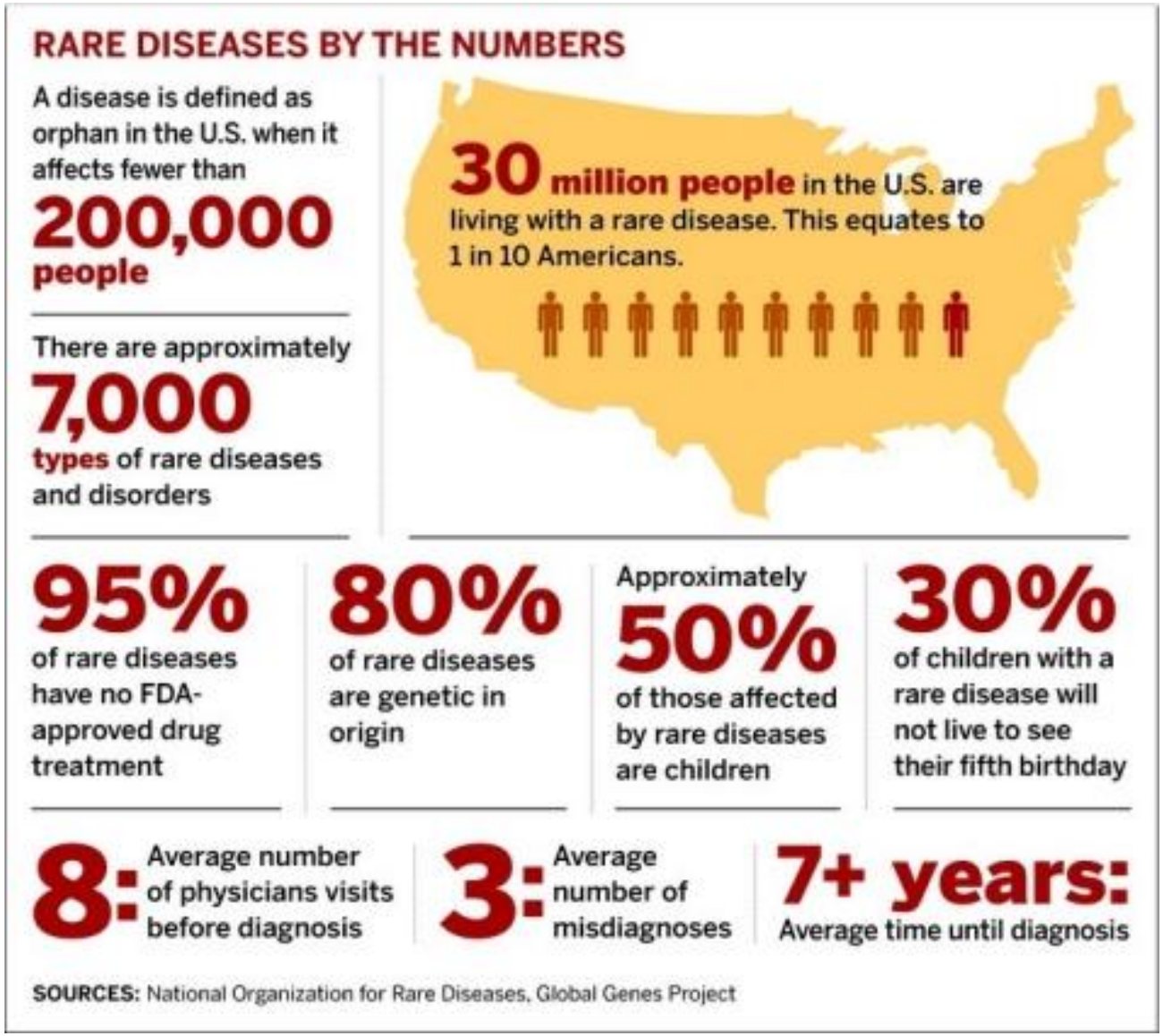
Outline

1. Background: TMAU as disease entity, the choline challenge test for diagnosis

2. Evaluation of individuals with malodor problems

3. Genetics of TMAU

Rare Diseases by the Numbers



Most Normal Human Body & Oral Odors Formed By Interactions of Skin Gland Secretions and Microorganisms

- **Scalp/Hair**
- **Mouth Breath**
- **Cerumen**
- **Axillae/Underams**
- **Chest**
- **Genital/Vaginal**
- **Feet**
- **Skin/Hands**

Prior to the 20th century and the wide-spread use of scented soaps and consumer products, it was more readily apparent that humans emit a variety of volatile odorous metabolites.

Lack of knowledge among health-care professionals surrounding TMAU may impede diagnosis*

- Most health professional training curricula (medical, nursing, etc.) fail to include the symptoms and causes of TMAU!
- Episodic intensity of odor often confuses the diagnosis.
- Inheritance of TMAU is often unclear to health providers, and genetic tests often are inconclusive: they may not demonstrate phenotype
- Don’t go to the “doctor down the street;” go to a major teaching hospital/medical center: genetic and metabolic disease specialists

***** Thanks to Dr. P.V. Fennessey

Lack of knowledge among health-care professionals surrounding TMAU may Impede diagnosis*

- Information is available
  - The Internet
  - Patient support groups
  - Other rare disease info on TV and the Web

Without these sources, many TMAU patients would still be in the dark about this genetic disease!

*Thanks to Dr. P.V. Fennessey

TMAU: some history*

- **1842 and 1858**
  - Two reports of TMAU-like disease (*Lancet)*
- **1970**
  - First clinical description: Humbert et al., in Denver (*Lancet)*
- **1970-1985**
  - Reports of isolated and sporadic cases
  - Data suggest diet plays an important role in the disease
- **1980-2000**
  - Genetic studies of N-oxidation (FMO3) and other cofactors
- **1995 to present**
  - Systematic recognition of this rare genetic disease

*Thanks to Dr. P.V. Fennessey

Measurement of Urinary TMA Concentration*

1980 - 1984: Total TMA (mg/mg creatinine)

(concentration depends on diet)

1984 - present: Total TMA before and after ingestion of choline test load

Ratio: (TMAO /TMA) x 100%

Normal TMAO > 95%
(ratio independent of diet)

Currently we provide: TMA & TMAO conc. as micromoles/millimole of creatinine as well as %TMAO.

University of Colorado, Dept. of Pediatrics, Biochemical Genetics Laboratory (www.DenverGenetics.org)

*Thanks to Dr. P.V. Fennessey

Causes of Variability in TMA Odor Intensity*

- Estimated production of TMA from turnover of intrinsic biomolecules:
  - Micrograms (0.001 mg)
- Estimated production of TMA from action of gut bacteria on natural products in the diet
  - Milligrams (>1.0 mg)
- **Difference of >1000x (depending on diet)**

*Thanks to Dr. P.V. Fennessey

Monell Patient Characteristics

1. ~1985-1995: many referred by physician or dentist

2. Internet: many now self-referred

3. Patients mostly from the U.S., but also from Canada, Honduras, Venezuela and the U.K.

4. Many have been to ≥ 4 clinical and/or dental specialists

5. All patients had multi-step exam involving both analytical and sensory techniques: the critical part is a choline challenge test to determine the diagnosis of TMAU.
6. Most of our in-house in vivo evaluations of patients were done between 1988 – 2008 (~ 350 individuals).
7. Starting around 2003 we began using a home testing kit; now almost all testing done this way

Large Undiagnosed Population of Individuals with Trimethylaminuria

- Diagnosed via Choline Challenge Test (CCT; Tjoa and Fennessey, Anal. Biochem.197:77-82, 1991)
- Trimethylamine (TMA) is a gas at body temperature and has a strong, pungent, offensive, fish-odor; at low concentrations it may be percieved as “foul” or “unpleasant” Reported to be found in all body fluids
- “Fish odor syndrome” should not be used. Only ~10% of our TMAU-positive individuals have this presentation.
- Symptoms are sporadic and may escape notice due to low choline intake or specific anosmia in the clinician (rare).

Trimethylaminuria Patients at Monell Center

- >350 individuals
- 111 (~ 32%) diagnosed with some form of TMAU (Dr. Reed will elaborate further)
- Average age of our TMAU-affected population is 43.6 years (range 3 to 79 years)

Patient Self-reports of Symptoms

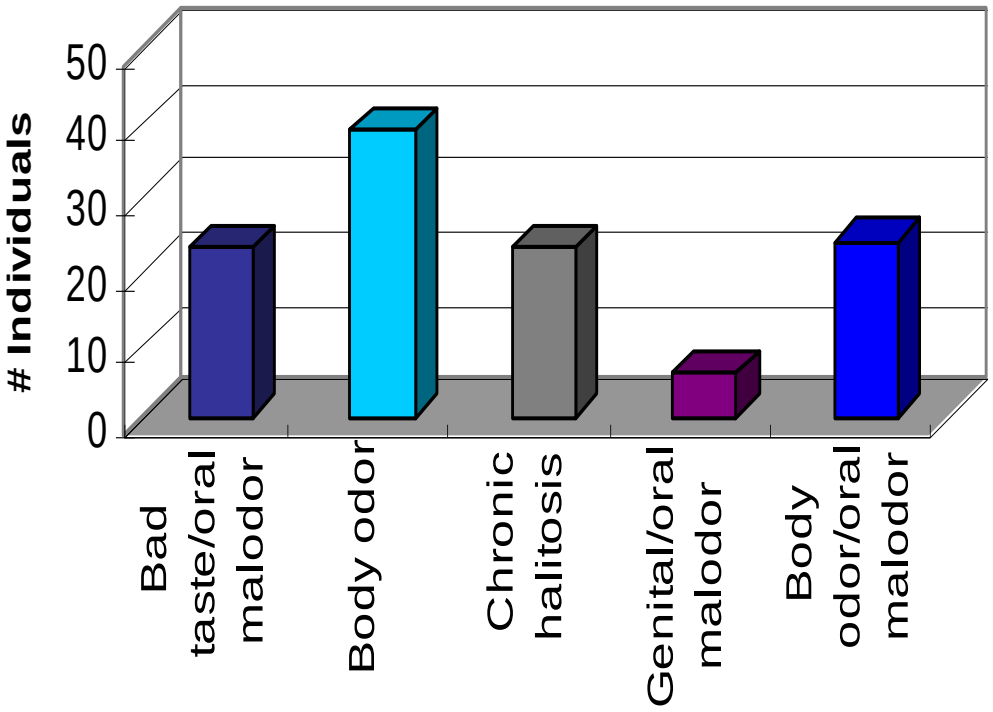
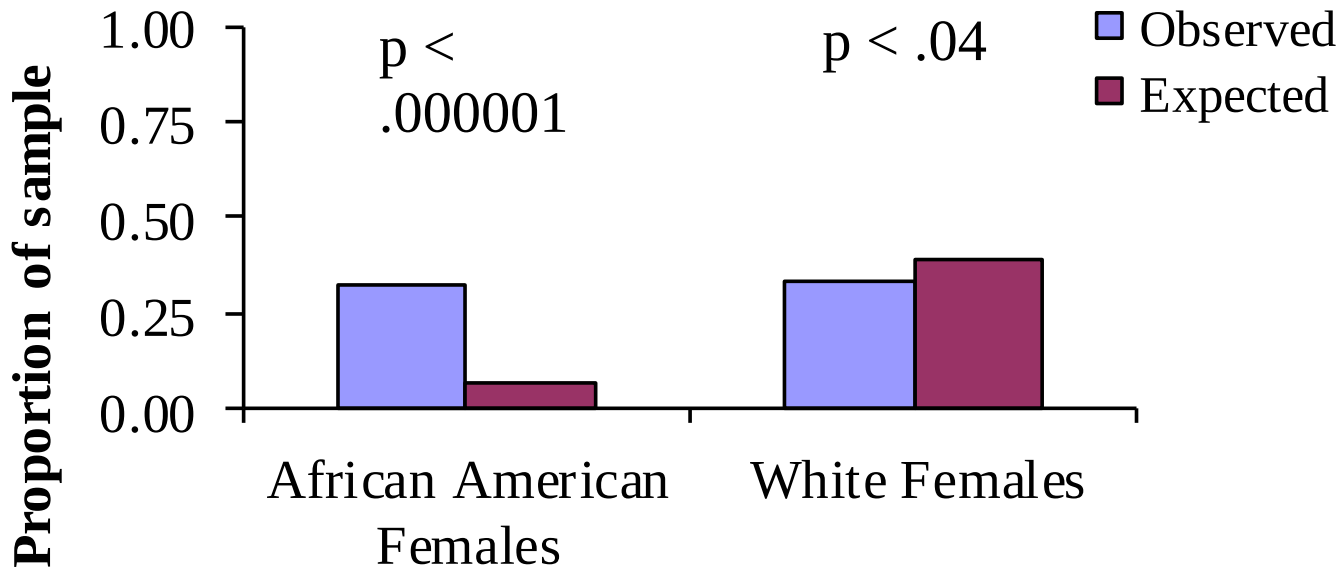
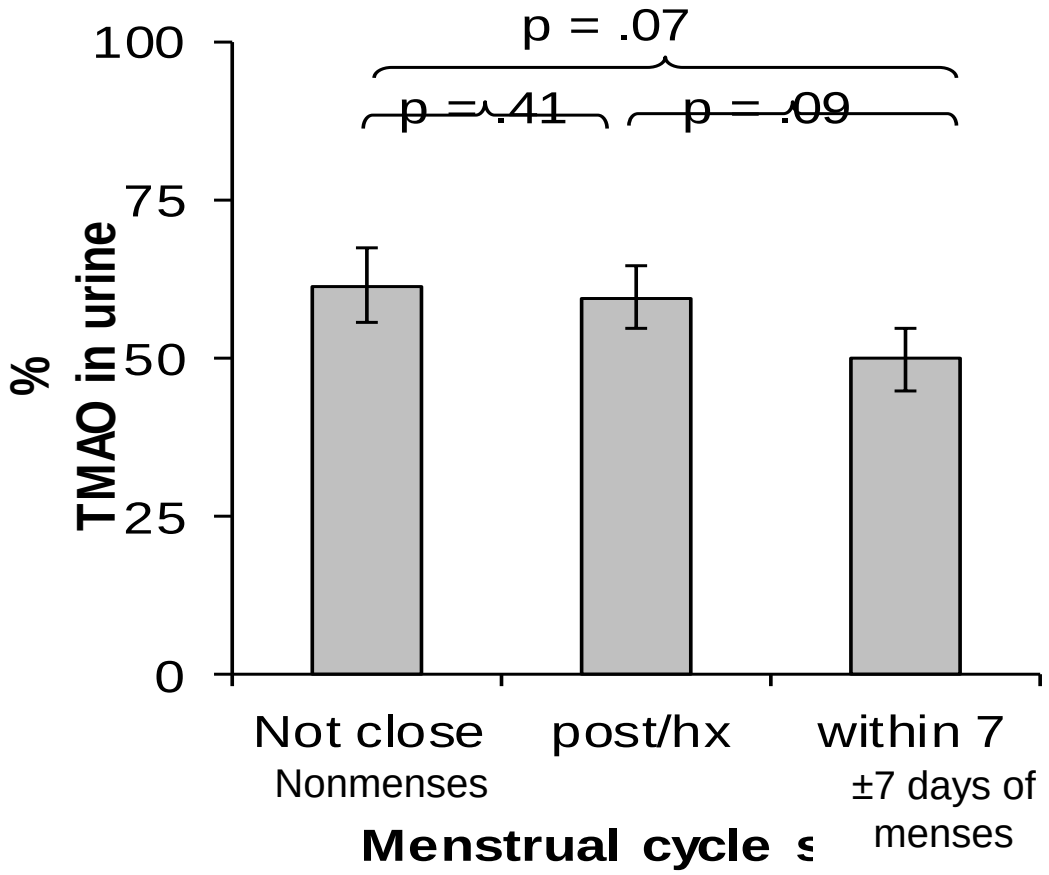


Figure 1. Presenting symptoms of TMAU-positive patients

3x More Women Than Men Are TMAU Positive
Many Are African-American



Females' Ability to Metabolize TMA Depends on where they are in their Menstrual Cycle



In both genders, variability in TMA Odor intensity can be linked to rate of production*

TMA appearance after a 5 g oral choline load (adult):

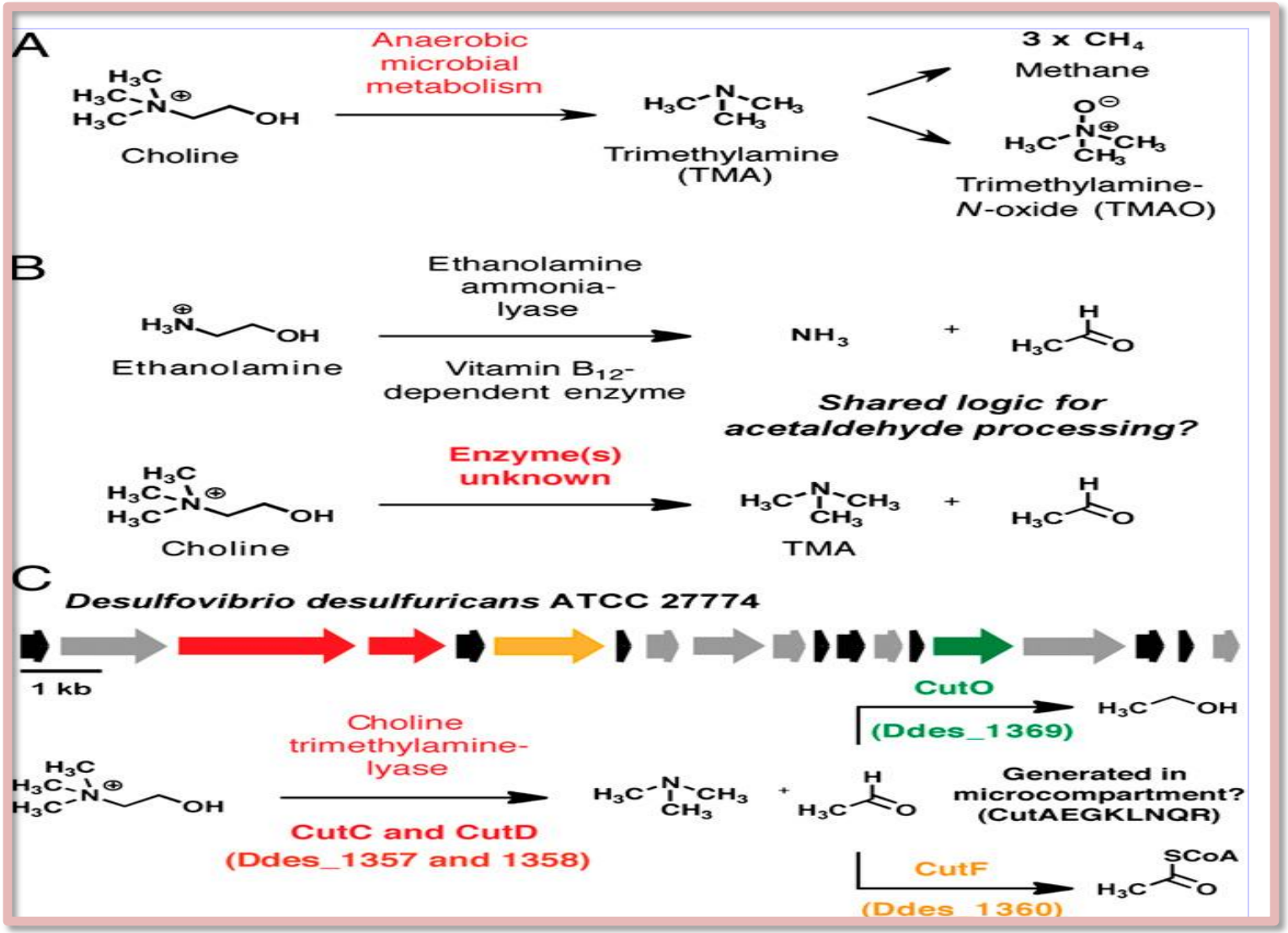
0 - 8 hours	**23%**	(rapid passage through gut)
8 - 16 hours	**55%**	(slow passage through gut)
16 - 24 hours	**22%**	(poor passage through gut)

Suggestion that bacteria in colon is cause of peak production

- Supported by literature reports/case studies of TMA suppression by antibiotics
- Also, how you perform the choline challenge is important
- As previous slide showed, for pre-menopausal females, when you test is important

* Adapted from Tjoa and Fennessey, 1991

Choline Utilization (Cut) Gene Cluster



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Looking ahead: can these be influenced?

- Proportion of gut bacteria with *Cut* enzymes
- Small molecule inhibitors of *Cut* enzymes
- Are these bacteria found elsewhere…? Most likely

TMAU: Non-Related Complications

1. Syndromes such as Prader-Willi and Noonan's
2. Skin Rashes
3. Seizures
4. Hypertension (severe, labile, moderate)
5. Psychiatric dysfunction…impaired metabolism of
6. N- and S- containing compounds
7. Depression
8. Sarcoidosis
9. IBS and other lower GI problems (??)
10. Females: recurring fishy vaginal odor not related to TMAU, e.g., *cut* enzyme-containing bacteria problem
11. Present in bacterial plaque on the tongue?

Most patients appear to lead normal lives & work at a variety of professions

Main problem: Psycho-social problems caused by odor production/symptoms.

Tied to individual personality

Summary

- Our results demonstrate the necessity to screen for TMAU with an objective, analytical test and not rely upon anyone's olfactory abilities.
- Only ~ 10% of patients with TMAU have had a fish-like or malodor during their exam
- Patients may not be aware of when odor is present or the intensity of their own odor.
- In our referred patient population, most patients have had a similar history. Many do not smell badly at all (organoleptic evaluation of breath, axillae, clothing items).
- Very few patients have high levels of odor-producing axillary bacteria (rel. to "normal") or much axillary odor
- Amelioration of symptoms:

  short term antibiotics, osmotic laxitives

  longer term choline & salt water fish restriction, OTC supplements.

For many "nothing works" without positive reinforcement: use an odor buddy

Summary…continued

- Both TMAU and non-TMAU patients may have bad breath caused by volatile sulfur compounds
  - 57% of TMAU-positive patients
  - 60% of non-TMAU patients

- Female patients
  - either more affected by TMAU
  - or present in greater numbers to a clinic for relief of symptoms
  - many are African-American

- Decreased FMO3 efficiency due to complications, e.g. viral infections/ drug intake.

- Funding needed for
  - follow-up
  - in-depth study of symptoms vs. treatment regimes.

- Etiology/Genetics/Other odor-producing genetic disorders ??

- My question to the audience: why are so many test kits requested but only 40-60% returned?