Genetic Testing & Counseling in Dementia: Guidance for Primary Care Providers

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Disclosure Statement

- No financial disclosures to report.

Learning Objectives

- Differentiate between genetic risk factors (like APOE) and monogenic causes of dementia.
- Demonstrate knowledge of genetic testing techniques and considerations of challenges of this testing.
- Identify appropriate clinical scenarios where genetic testing for monogenic dementia should be considered.
- Understand the clinical utility, limitations, and key counseling points for patients undergoing genetic testing.
- Apply principles of ethical communication and follow-up, especially regarding psychosocial impact and insurance.

Why Genetic Testing in Dementia is Relevant in Primary Care Now

- **Expanded Access:** Advances in genes and biomarkers now allow adults to undergo testing to learn about their risk for Alzheimer disease (AD).
- **Routes to Testing:** Patients are obtaining results through direct-to-consumer (DTC) services as part of large panels.
- **Limited Guidance:** Expanded access, combined with limited guidance from DTC companies, means more adults are consulting their PCPs about these results.
- **Therapeutic Implications:** Genetic status may factor into candidacy decisions for emerging therapies.

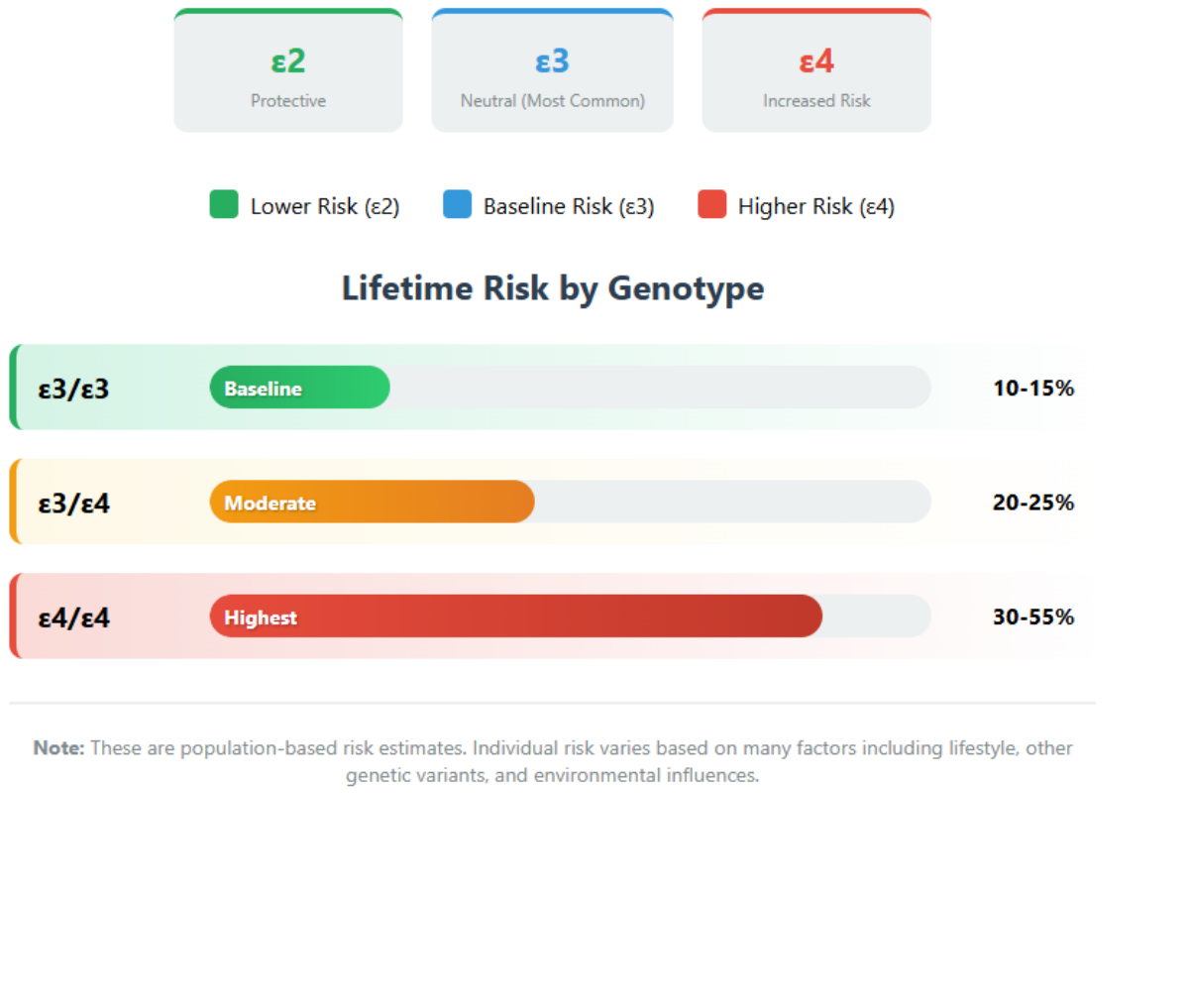
Two Types of Genetic Contribution to Dementia

Category	Mendelian (Monogenic) Dementia	Complex/Polygenic Risk Factors
Description	Caused by a variant in a **single gene**.	Caused by **many genetic variations of small effect** interacting with environmental factors.
Inheritance	Autosomal dominant with high penetrance	Not straightforward; complex interplay of factors.
Penetrance/Risk	**Deterministic:** Carriers may have a lifetime risk generally over 95%.	**Risk Factor:** Increases susceptibility but is **neither necessary nor sufficient** to cause the disease.
Examples	*APP, PSEN1, PSEN2* (AD); *C9orf72, GRN, MAPT* (FTD); *NOTCH3, HTRA1, GLA* (VaD); *HTT* (HD); *PRNP (Prion)*	*APOE* e4 allele (AD); *GBA* (LBD)

Risk Factor Testing: APOE Gene

Understanding the APOE Gene and Risk

- APOE gene variants are a known risk factor for late-onset AD or Mild Cognitive Impairment (MCI).
- A person has 2 alleles (copies), 3 common variants: e2, e3, e4



APOE: Testing & Counseling

Current Standards of Care

Professional societies recommend against routine APOE testing

Limited clinical utility due to lack of targeted interventions

Results don't significantly alter standard dementia prevention strategies

Key Counseling Concepts

Genetic Risk ≠ Genetic Fate: Even highest-risk genotype (ε4/ε4) leaves 45-70% unaffected

Balanced Risk Communication: Always present reciprocal probabilities to reduce patient anxiety and cognitive bias

Example: "Your risk is 30-55%, meaning your chance of NOT developing AD is 45-70%"

Emerging Clinical Applications

Anti-Amyloid Therapy Selection: APOE status critical for ARIA risk assessment

ε4/ε4 Patients: Require intensive monitoring due to elevated ARIA susceptibility

ARIA Consequences: Brain edema, hemorrhage, potentially fatal outcomes

Monogenic Dementia

Key Genes Associated with Monogenic Dementia

- **Autosomal Dominant Alzheimer Disease (AD):**
  - PSEN1 (most frequent, 30%-70% of familial AD). Associated with earlier onset (30-60 years).
  - APP (10%-15%). Can cause cerebral amyloid angiopathy (CAA) leading to haemorrhage.
  - PSEN2 (least common). Associated with later, more variable onset (50-65 years).
- **Frontotemporal Dementia (FTD)** (more than dozen genes associated):
  - C9orf72: Hexanucleotide repeat expansions account for the majority of familial FTD/MND spectrum.
  - GRN (Progranulin): Associated with bvFTD or nonfluent PPA.
  - MAPT (Microtubule-associated protein tau): Highly penetrant and often associated with parkinsonism or FTD overlap syndromes.
- **Vascular Dementia (VaD)** (examples of small vessel disease)**:**
  - NOTCH3: CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy), causing symptoms such as migraines with aura, strokes, and dementia
  - HTRA1: CARASIL (Cerebral Autosomal Recessive Arteriopathy with Subcortical Infarcts and Leukoencephalopathy), causing symptoms such as alopecia, spasticity, spondylosis, strokes, and dementia
  - GLA: Fabry disease, can affect various organs including kidneys, heart, and nervous system
- **Other Deterministic Dementias:**
  - Huntington's Disease (HTT) and Prion Disease (PRNP) typically warrant single-gene testing due to distinctive presentations.
  - Lewy Body Disorders (DLB/PDD) are mostly sporadic/polygenic, some genetic risk factors have been identified (GBA or SNCA)

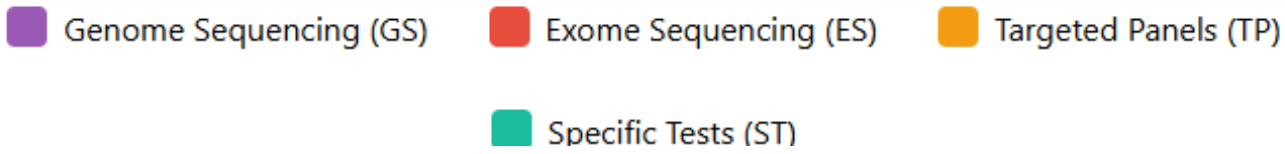
When to Consider Monogenic Testing

Indication	Description/Rationale
Age at Onset	**Early Onset Dementia (EOD):** Onset typically **before age 65 years**. • Onset between 20-64 years: approx. **15%-20%** chance of a pathogenic variant. • Onset <51 years, even sporadically, shows 12.3% chance (especially *PSEN1*).
Family History	**Strong Mendelian Pattern:** Multiple affected members in consecutive generations. • A strong family history can equate to a **45%-88%** chance of finding a pathogenic variant.
Phenotype Clues	**Specific clinical syndromes:** e.g. Behavioural Variant FTD (bvFTD) or FTD-ALS
Diagnostic Clarity/Uncertainty	Identification of a disease-causing variant can **provide a precise diagnosis** (particularly for atypical phenotypes), reduce need for further investigation, and provide clarify for more accurate prognosis
Requirement for Clinical Trial Eligibility	E.g. amyloid-β antibody therapy in AD, GRN replacement in FTD, and gene-silencing in HD

Genetic Testing Techniques

Comparative Analysis

Testing Method	Genomic Coverage	Cost	Complexity	Best Use Cases
Genome Sequencing	100%	$$$$	High	Unknown disorders, research, comprehensive analysis
Exome Sequencing	~2%	$$$	Medium	Rare diseases, Mendelian disorders
Targeted Panels	<0.1%	$$	Low	Specific phenotypes, clinical diagnosis
Specific Tests	Single locus	$	Low	Known variants, repeat expansions, CNVs



Choosing the Right Test

- **Recommendation:** Due to the clinical heterogeneity and pleiotropy (one gene causing multiple phenotypes, or multiple genes causing one phenotype) in AD and FTD, single-gene testing is generally not recommended (except for highly distinctive disorders like HD).
- **Preferred Methods:** Targeted multigene panels, exome sequencing (ES), or genome sequencing (GS) are the most appropriate choices.
  - ES/GS allow for re-analysis as new genetic information emerges
- **Technical Limitation:** Standard next-generation sequencing (NGS) platforms are typically poor at detecting large deletions, copy number variants, and certain tandem repeat expansions.
  - Specifically, C9orf72 expansions and APP/SNCA duplications may require supplementary PCR-based testing or chromosomal microarray.

Genetic Testing Challanges

- **Insurance coverage is poor –** many patients (families) will pay out of pocket for the entirety of the genetic test
- **Results are not just positive or negative**
  - Pathogenic, likely-pathogenic, variant of uncertain significance, likely benign, benign
  - Pathogenic (full penetrance), reduced penetrance, intermediate, normal
- **Variable expression** (inter- and intra-familial variability)
- **Low detection rates –** negative does not rule out genetics

Counseling &
Other Considerations

Genetic Counseling is Crucial

- **Genetic testing in dementia can profoundly impact patients, families, and life decisions.**
- Pre-test counseling: foundation for informed decisions
  - Review of risks, benefits, and limitations including insurance risks; psychological preparation; informed consent
- Post-test counseling: navigating results
  - Result interpretation, risk communication, adapting to results and care planning, family implications
- Psychological support throughout (e.g. distress caused by results, both negative and positive; long-term support)

Utility of a Confirmed Genetic Diagnosis

Genetic testing, especially for symptomatic patients, is not without risk, but a positive finding offers several advantages:

- **Diagnostic Clarity:** Provides a precise diagnosis, often simplifying the diagnostic odyssey and avoiding the need for further investigations (e.g., serial neuroimaging).
- **Prognostic Information:** Helps confirm the clinical diagnosis and informs the likely disease trajectory.
- **Treatment Access:** Allows access to therapies or clinical trials targeted to the specific mutation (e.g., anti-amyloid trials in AD or GRN replacement therapy in FTD).
- **Family Planning/Autonomy:** Provides information for at-risk relatives to consider predictive testing, reproductive options (e.g., Preimplantation Genetic Diagnosis [PGD]), or life choices.

Understanding Patient Decision-Making

- **Intuition Over Fact:** Patients and families often make decisions about testing based on quick, intuitive, value-driven judgments, rather than extensive deliberation of factual information.
- **Primary Motivation is Altruism:** The majority of individuals pursuing testing are motivated by the perceived benefit to their families (58% in one study).
    - E.g. Motivations include providing information to children about heredity, enhancing personal and medical actionability, and resolving uncertainty.

Psychosocial Risks & Challenges

- **Psychological Distress:** Learning genetic status (positive or negative) can cause anxiety, depression, hopelessness, or suicidal ideation.
  - In cases of unexpected DTC results, distress and anxiety are heightened.
- **Family Conflict:** Genetic information disclosure is complex and can be influenced by pre-existing family dynamics or differing coping strategies (avoidance vs. information-seeking). Concerns include the emotional burden on relatives and the potential for straining family relationships.
- **Uncertainty**: Results often include Variants of Uncertain Significance (VUS), which are difficult to process psychologically, as the evidence is insufficient or conflicting to classify them as pathogenic or benign.

Considerations for Primary Care

- Capacity and Consent: Obtaining informed consent from patients with cognitive impairment is challenging. Testing a patient who lacks capacity should be based on their best interests (e.g., informing diagnosis/treatment, or informing relatives' risk).
- Confidentiality vs. Duty to Inform: Clinicians must balance the patient's right to confidentiality with the right of an interested third party (relatives) to be informed of life-altering results.
- Insurance Risk (Documentation Caution): Documented conversations about genetic test results in the medical record may become part of a patient's application for long-term care, disability, or life insurance.
- Referral: Refer to a genetic counselor or other specialist to provide patients with access to added expertise and guidance, especially for complex cases, VUS interpretation, or decisions involving family planning.
- Address Stigma: Correct misinformation and adjust patient expectations that may be false or exaggerated.

Considerations for Primary Care cont.

- **Predictive (deterministic) genetic testing considerations:**
  - Age-appropriate testing
    - Avoid testing minors for adult-onset disorders.
  - Psychological readiness assessment
    - Screen for depression, anxiety, or poor coping mechanisms before testing.
  - Family system impact
    - Consider testing's effect on family dynamics, relationships, and reproductive decisions.
  - Long-term follow-up planning
    - Establish plans for ongoing care of patients with positive predictive results.

Landscape of Genetic Services

Genetic services in the PNW are most available in urban settings.

Regional Medical Genetics Clinics*

Washington

* Sacred Heart Genetics (Spokane)
* Seattle Children's (Seattle & Satellite Clinics)
* Swedish & Providence (Seattle & Puget Sound)
* University of Washington (Seattle)
* Kaiser Permanente (Seattle)
* Mary Bridge Genetics (Tacoma & Satellite Clinics)

Oregon

* OHSU (Portland)
* Legacy (Portland)
* Kaiser Permanente (Portland)

Idaho

* St. Luke's Children's Hospital (Boise)

Alaska

* State of Alaska Metabolic Clinic (rotating locations)

Montana

* Shodair Children's Hospital (Helena & Satellite Clinics)

Utah

* University of Utah (Salt Lake City)

*Examples of localization of genetic services.
Does not account for all prenatal and cancer genetic services.

Case Vignettes

Case #1: Managing APOE e4 results from DTC

A. Patient is a 65 yo female with no health or cognitive concerns. Family history of Alzheimer's disease in mother, diagnosed in her 70s. Patient recently did DTC testing and found she is positive for one e4 allele (e4). She is very concerned about developing AD.

A. Patient is a 40 yo male who did DTC testing for health & wellness and found he is positive for two e4 alleles (e4 / e4). He wants to know what he can do to lower his risks of dementia.

Case #1: Managing APOE e4 results from DTC

- Considerations
  - DTC testing provided results with no pre- or post-test counseling
  - Psychological impact of unexpected results
  - APOE status is a risk factor, not deterministic
  - Need for probabilistic risk communication
  - Emphasis on actionable lifestyle factors
  - Consideration of documentation & concerns for discrimination
  - Identification of resources
  - Referrals for additional assessments and support

Case #2: Strong suspicion of familial FTD

- Patient is a 55 yo female with recent diagnosis of FTD. Her father was estranged from the family and passed away from unknown causes at 52 yo. Her paternal uncle passed away at age 60 from ALS. She has four adult children who are concerned about their risk and future planning.

- Genetic testing is done and identifies

Case #2: Strong suspicion of familial FTD

- Considerations
  - High likelihood of monogenic (familial) causes based on early age of onset & family history
  - Need for genetic testing
  - Motivation is driven by family benefit / reproductive options
  - Determining best interests
  - Identification of resources
  - Referrals for additional assessments and support

Case #2: Familial FTD cont.

- Patient is a 55 yo female with recent diagnosis of FTD. Her father was estranged from the family and passed away from unknown causes at 52 yo. Her paternal uncle passed away at age 60 from ALS. She has four adult children who are concerned about their risk and future planning.

- Genetic testing is done and identifies a C9orf72 repeat expansion. Two children want testing, one has no interest, and one is undecided. The who is undecided has a history of severe depression and suicide attempts.

Case #2: Familial FTD cont.

- Considerations
  - Family members have different preferences about genetic testing
  - Mental health concerns for high-risk relatives
  - Family / reproductive planning implications
  - Insurance and employment discrimination

Case #3: “Predictive” testing & duty to warn

- Patient is a 48 yo male whose mother passed away from early-onset dementia in her 60s. He reports no health or memory concerns, but during the visit you learn he was recently put on forced medical leave due to performance concerns at work. He expresses uncertainty about genetic testing, but after discussion he opts to proceed. Genetic testing reveals a disease-causing variant in the gene PSEN1. When results are disclosed, he responds that he does not believe the results and requests the results not be shared with anyone, including his family.

Case #3: “Predictive” testing & duty to warn

- Considerations
  - Psychological readiness for genetic testing
  - Implications for family members & their decision making
  - Confidentiality & duty to warn
  - Impact on insurance and employment
  - Identification of resources
  - Referrals for additional assessments and support
  - Ongoing follow-up care

Case #4: Family history late-onset dementia

- Patient is a 67 yo female who has concerns about her family history. Her father developed Alzheimer's disease in his early 80s and her older sister recently was diagnosed at age 76. She is worried she is "next in line" and requests genetic testing to know if she will also develop dementia. She reports no memory problems and her cognitive screen in clinic is normal.

Case #4: Family history late-onset dementia

- Considerations
  - Genetic testing is often not indicated in late-onset cases
  - Supportive counseling
  - Emphasis on actionable lifestyle factors
  - Identification of resources
  - Referrals for additional assessments and support

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