Aspetti etici delle indagini genetiche

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www.univacalabria.it

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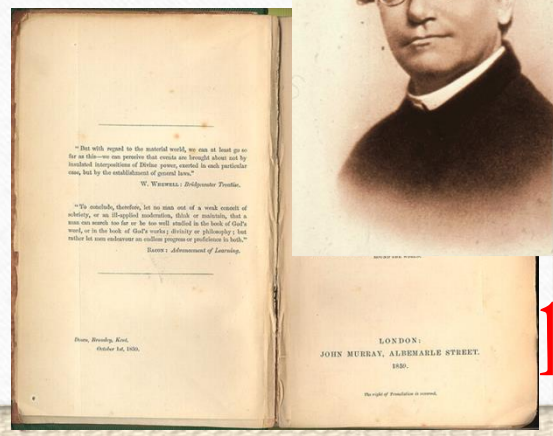
Per millenni l'avanzamento delle conoscenze è stato lentissimo

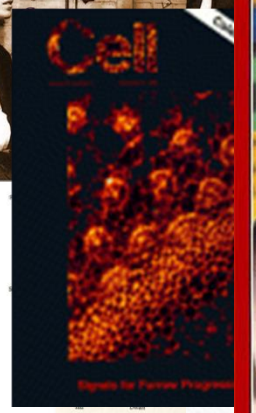
Darwin
1859

Leggi di Mendel
1865

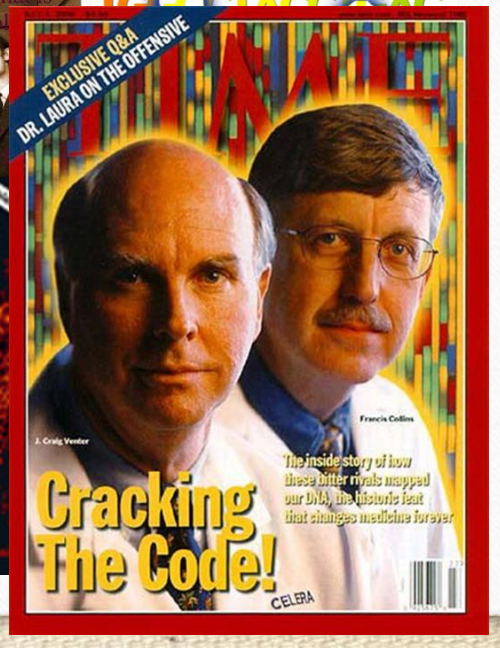


Doppia Elica
Watson & C
1953

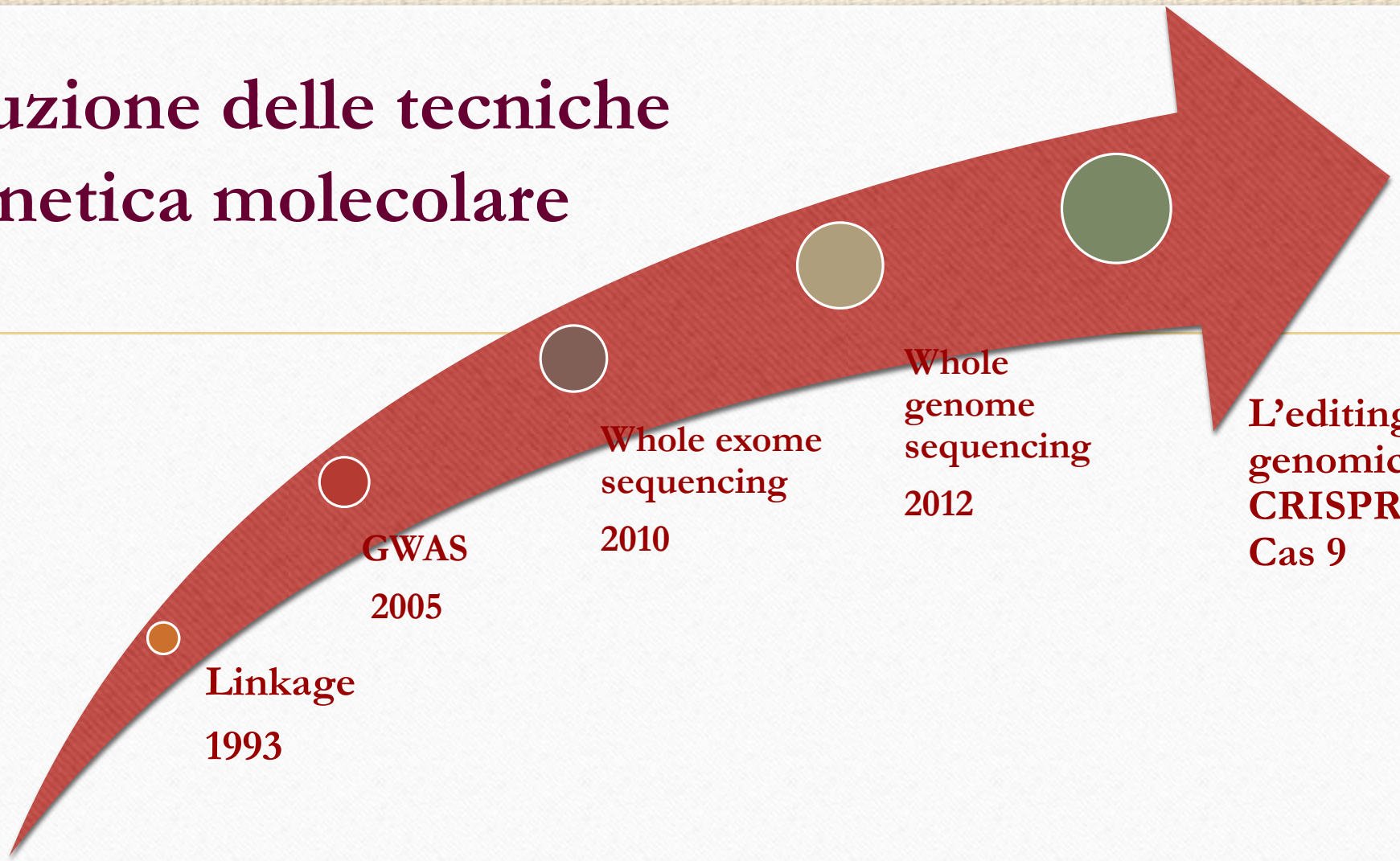
Scoperta del gene dell'Huntington 1993



Decodifica del genoma umano 2001



Evoluzione delle tecniche di genetica molecolare



Dichiarazione dei diritti dell'uomo

1948

Dichiarazione universale sul genoma umano e i diritti umani (1997)

- …Riconoscendo che le ricerche sul genoma umano e le loro applicazioni aprono immense prospettive di miglioramento della salute degli individui e dell'umanità tutta, (…) sottolinea che esse devono allo stesso tempo rispettare pienamente la dignità, la libertà ed i diritti dell'uomo, come pure il divieto di ogni forma di discriminazione fondata sulle caratteristiche genetiche

Necessità di conciliare l'interesse della collettività allo sviluppo della ricerca scientifica con il diritto dell'individuo alla tutela della propria dignità e libertà (art. 2).

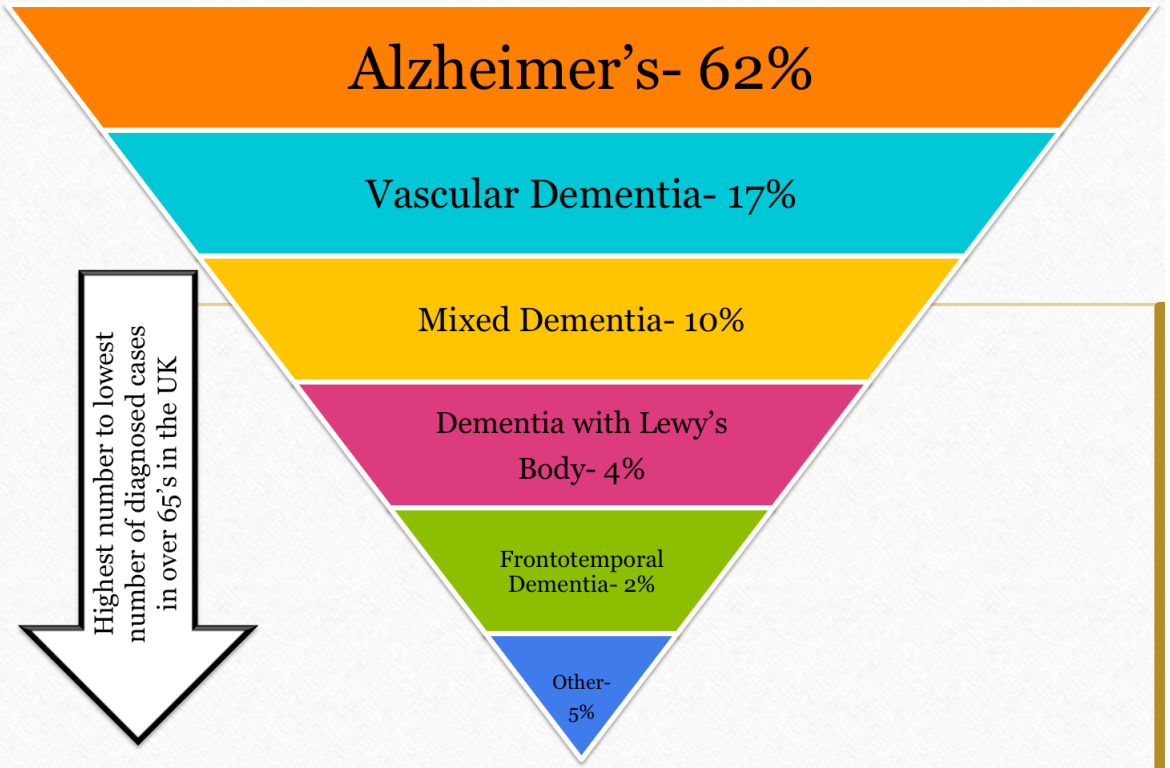
Data di adozione
11/11/1997

Diritti individuali per la tutela delle persone interessate o toccate dalla raccolta e dal trattamento delle informazioni genetiche

- **Necessità del consenso** preliminare, libero ed informato allo svolgimento di ricerche o diagnosi (art. 5, lett. b);
- **Diritto di conoscere o di ignorare il risultato dei test genetici** (art. 5, lett. c);
- **Protezione dei dati genetici** (art. 7).
- Il medico può comunicare i risultati di un esame genetico solo alla persona interessata o, se quest'ultima è incapace di discernimento, al suo rappresentante legale (art.19). Il medico può comunicare i risultati dell'esame ai familiari, al coniuge o al partner se la persona interessata vi acconsente espressamente. Se il consenso è negato, il medico può chiedere all'autorità competente di essere sciolto dal segreto professionale, giusta l'articolo 321 numero 2 del Codice penale 6, se ciò è necessario per tutelare gli interessi preponderanti dei familiari, del coniuge o del partner. L'autorità competente può chiedere il parere della Commissione di esperti per gli esami genetici sull'essere umano. L'elaborazione di dati genetici soggiace:
- a) al segreto professionale giusta gli articoli 321 e 321bis del Codice penale; e b) alle disposizioni federali e cantonali relative alla protezione dei dati.

Dichiarazione dei diritti umani 1997

Cosa significa tutto questo nel campo delle demenze e delle malattie neurodegenerative ???
E di che test parliamo???



Kunkle B et al JAMANeurol. doi:10.1001/jamaneurol.2017.1518 PublishedonlineJuly24,2017.

Mutations in *APP*, *PSEN1*, and *PSEN2* lead to early-onset Alzheimer disease (EOAD) but account for only approximately 11% of EOAD overall, leaving most of the genetic risk for the most severe form of Alzheimer disease unexplained. This extreme phenotype likely harbors highly penetrant risk variants, making it primed for discovery of novel risk genes and pathways for AD.

Harvey RJ, Skelton-Robinson M, Rossor MN. The and causes of dementia in people under the age of 65 years. J Neurol Neurosurg Psychiatr 2003;74:1206–09.

Dementia autosomal dominant genes

Alzheimer Disease & Frontotemporal Dementia Mutation Database

Home | AD&FTDMDB | Links | About

Lookup Mutations
- By Gene
- By Phenotype
- By Publication
- Latest Updates

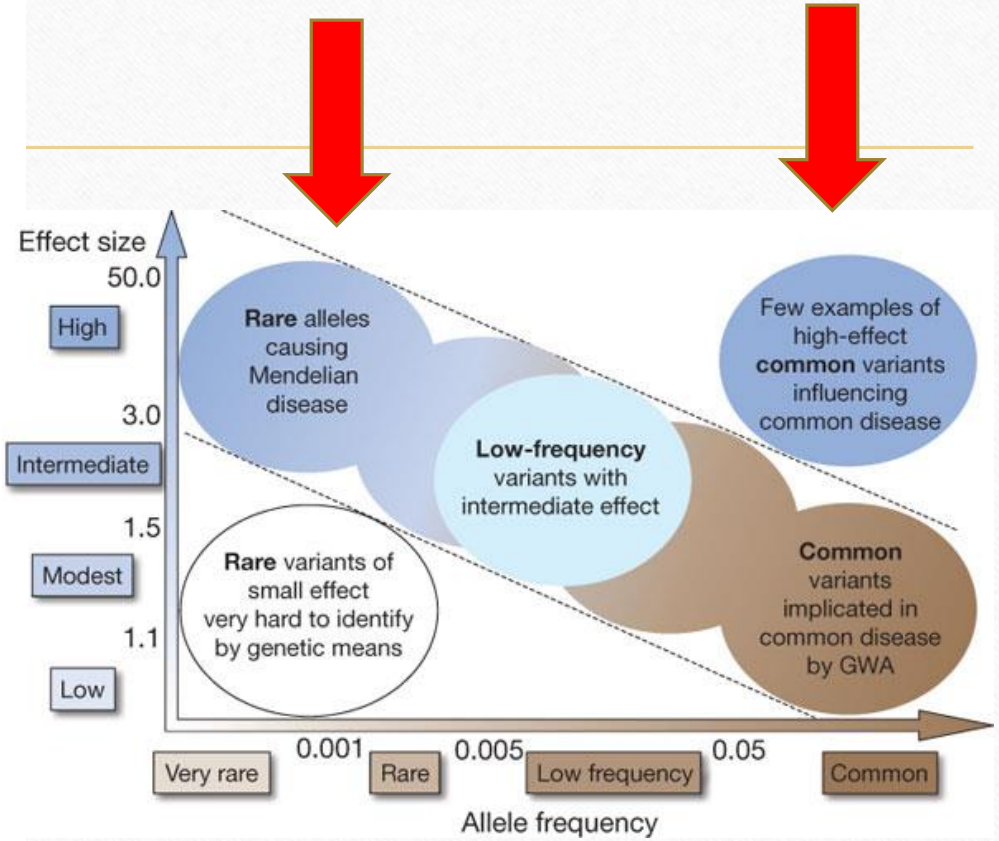
Statistics
- Per Gene
- Per Exon
- Per Domain

Submit Mutations

Mutations per Gene

Gene	# Mutations	# Families
APP	33 (7.78 %)	90 (6.20 %)
PSEN1	185 (43.63 %)	405 (27.91 %)
PSEN2	13 (3.07 %)	22 (1.52 %)
C9orf72	1 (0.24 %)	336 (23.16 %)
CHMP2B	4 (0.94 %)	5 (0.34 %)
FUS	23 (5.42 %)	49 (3.38 %)
GRN	69 (16.27 %)	231 (15.92 %)
MAPT	44 (10.38 %)	134 (9.24 %)
TARDBP	34 (8.02 %)	131 (9.03 %)
VCP	18 (4.25 %)	48 (3.31 %)
Total	424	1451

AD&FTD mutation database



TA Manolio *et al. Nature* **461**, 747-753 (2009) doi:10.1038/nature08494

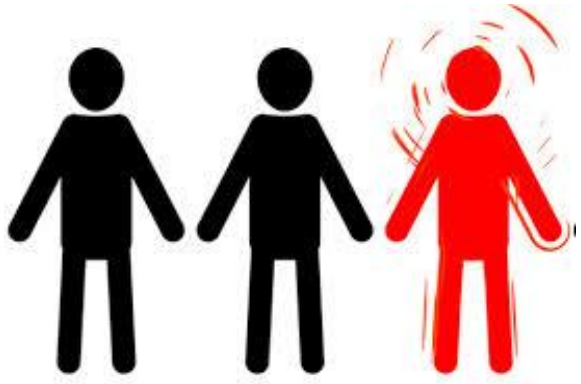
- **ALL GENETIC FORMS have to be considered RARE……(No more than 5 /10.000 persons)**

Alzheimer disease with Dominant transmission (ADAD) : **less than 0.1 % of ALL AD** is caused by one of the three genes.

Estimated prevalence 0.05/10.000

(PSEN1, OMIM *104311; PSEN2 OMIM *600759; APP OMIM *104760)

(*Tol et al., 1999; Sleegers et al.,2004; (Cruts et al., 2012*).



Frontotemporal dementia: 0.04 of familial FTLD is genetic

Estimated prevalence 0.2 /10.000

(MAPT *OMIM *157140*; GRN *OMIM *138945*; C9ORF72 *OMIM *614260;* CHMP-2B OMIM *609512; VCP OMIM *601023; FUS OMIM *137070)

Goldman JS et al., 2005; Goldman JS et al., 2007; van Swieten JC et al., 2008, Cruts et al., 2012

Questions ….

My mother, my grandmother, and a maternal aunt died at a young age from dementia. What risk do I have of developing the same disease?

My father had Alzheimer's at age 65. If I live past this age, will I have overcome the risk of developing the disease?

My mother has Alzheimer's and she has tested positive for APOE4. I want to know if I am at risk for the disease. I want to be tested.

Genetics in Degenerative Dementia

Current Status and Applicability

Amalia C. Bruni, MD, Maria E. Conidi, PhD, and Livia Bernardi, PhD

(*Alzheimer Dis Assoc Disord* 2014;00:000–000)

Tipologie di tests genetici

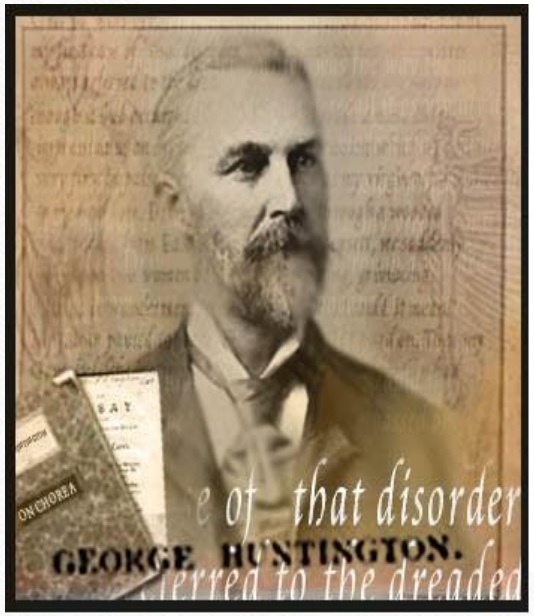
- **- Test diagnostici**, finalizzati a effettuare una diagnosi o di confermare, in una persona affetta, un sospetto clinico.
- - Test di identificazione dei portatori sani, finalizzati a individuare mutazioni comuni in specifici gruppi etnici, attraverso screening di popolazione (anche in epoca neonatale), oppure a svolgere indagini "a cascata" sui familiari a rischio di soggetti affetti da patologie genetiche in cui siano state individuate le mutazioni causali.
- - **Test preclinici o presintomatici**, finalizzati a identificare mutazioni responsabili di malattie genetiche, i cui sintomi non presenti alla nascita, compaiono (nel 100% dei casi) in epoche più tardive della vita.
-

- **- Test di suscettibilità**, finalizzati a individuare i **genotipi** che di per sé non causano una malattia, ma **comportano un aumentato rischio di svilupparla** in seguito all'esposizione a fattori ambientali favorenti o alla presenza di altri fattori genetici scatenanti. Rientra in questo ambito la maggior parte delle malattie multifattoriali dell'adulto. E' perciò importante stabilire il valore predittivo del test utilizzato. Il risultato del test genetico può solo evidenziare un rischio aumentato o diminuito di contrarre una malattia, rispetto alla popolazione.
- - **Test farmacogenetici**, finalizzati alla identificazione di variazioni di sequenza nel DNA, **in grado di predire la risposta "individuale"** ai farmaci, in termini di efficacia e di rischio relativo

La genetica applicata alle demenze

J Med Genet 1994;31:555–559

Clinical practice in medical genetics



Guidelines for the molecular genetics predictive test in Huntington's disease

Audrey Tyler (UK)*, Ralph Walker (Canada), Loe Went (Holland)*†, Nancy Wexler (USA)*.

Recommendations concerning the use of a predictive test for the detection of Huntington's disease (HD) were drawn up by a committee consisting of representatives of both the International Huntington Association (IHA) and the World Federation of Neurology (WFN) Re-

The committee is very much ind
Somviele (Belgium), who has been
years.

modello al quale la collettività scientifica si è ispirata per disegnare i comportamenti operativi e le linee guida per altre demenze le cui cause siano mutazioni dominanti.

Cosa cambia sapere
se la demenza è genetica???

Quale il vantaggio
per il paziente ?

E per la famiglia?

Cosa dicono le società scientifiche nel mondo.....

European Journal of Neurology 2007, 14: e1–e26 doi:10.1111/j.1468-1331.2006.01605.x

EFNS TASK FORCE/CME ARTICLE

Recommendations for the diagnosis and management of Alzheimer's disease and other disorders associated with dementia: EFNS guideline

G. Waldemar[a], B. Dubois[b], M. Emre[c], J. Georges[d], I. G. McKeith[e], M. Rossor[f], P. Scheltens[g], P. Tariska[h] and B. Winblad[i]

Recommendations: genetic testing

Screening for known pathogenic mutations can be undertaken in patients with appropriate phenotype or a family history of an autosomal dominant dementia. This should only be undertaken in specialist centres with appropriate counselling of the patient and family caregivers, and with consent *(Good Practice Point)*.

Pre-symptomatic testing may be performed in adults where there is a clear family history, and when there is a known mutation in an affected individual to ensure that a negative result is clinically significant. It is recommended that the Huntington's disease protocol is followed *(Good Practice Point)*.

Routine Apo E genotyping is not recommended *(Level B)*.

European Journal of Neurology 2010, **17**: 1236–1248 doi:10.1111/j.1468-1331.2010.03040.x

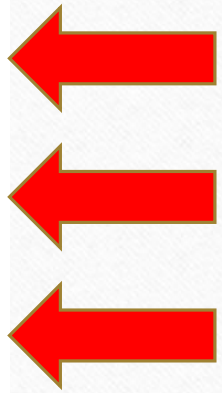
EFNS GUIDELINES/CME ARTICLE

EFNS guidelines for the diagnosis and management of Alzheimer's disease

J. Hort[a], J. T. O'Brien[b], G. Gainotti[c], T. Pirttila[d,†], B. O. Popescu[e], I. Rektorova[f], S. Sorbi[g] and P. Scheltens[h] on behalf of the EFNS Scientist Panel on Dementia

Genetic testing

The genetics of dementia is complex and genetic testing is associated with many ethical concerns. APP, PS1 and PS2 gene mutations explain 50% of the familial form of early-onset AD [53]. The ApoE ϵ4 allele is the only genetic factor consistently implicated in late-onset AD, but it is neither necessary nor sufficient for development of the disease [54]. Hence, there is no evidence to suggest ApoE testing is useful in a diagnostic setting. Autopsy diagnosis in familial dementias can be valuable for subsequent diagnosis and counselling. Testing of patients with familial dementia and of unaffected at-risk-relatives should be accompanied by neurogenetic counselling and undertaken only after full consent and by specialist centres. Pre-symptomatic testing may be performed in at risk member of family-carrying mutation. It is recommended that the Huntington's disease protocol is followed for pre-symptomatic testing [55].



ELSEVIER

Alzheimer's & Dementia ■ (2011) 1–7

Alzheimer's & Dementia

The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging and the Alzheimer's Association workgroup

Guy M. McKhann[a,b,*], David S. Knopman[c], Howard Chertkow[d,e], Bradley T. Hyman[f], Clifford R. Jack, Jr.[g], Claudia H. Kawas[h,i,j], William E. Klunk[k], Walter J. Koroshetz[l], Jennifer J. Manly[m,n,o], Richard Mayeux[m,n,o], Richard C. Mohs[p], John C. Morris[q], Martin N. Rossor[r], Philip Scheltens[s], Maria C. Carillo[t], Bill Thies[t], Sandra Weintraub[u,v], Creighton H. Phelps[w]

2011

4.2. Probable AD dementia with increased level of certainty

4.2.1. Probable AD dementia with documented decline

In persons who meet the core clinical criteria for probable AD dementia, documented cognitive decline increases the certainty that the condition represents an active, evolving pathologic process, but it does not specifically increase the certainty that the process is that of AD pathophysiology.

Probable AD dementia with documented decline is defined as follows: evidence of progressive cognitive decline on subsequent evaluations based on information from informants and cognitive testing in the context of either formal neuropsychological evaluation or standardized mental status examinations.

4.2.2. Probable AD dementia in a carrier of a causative AD genetic mutation

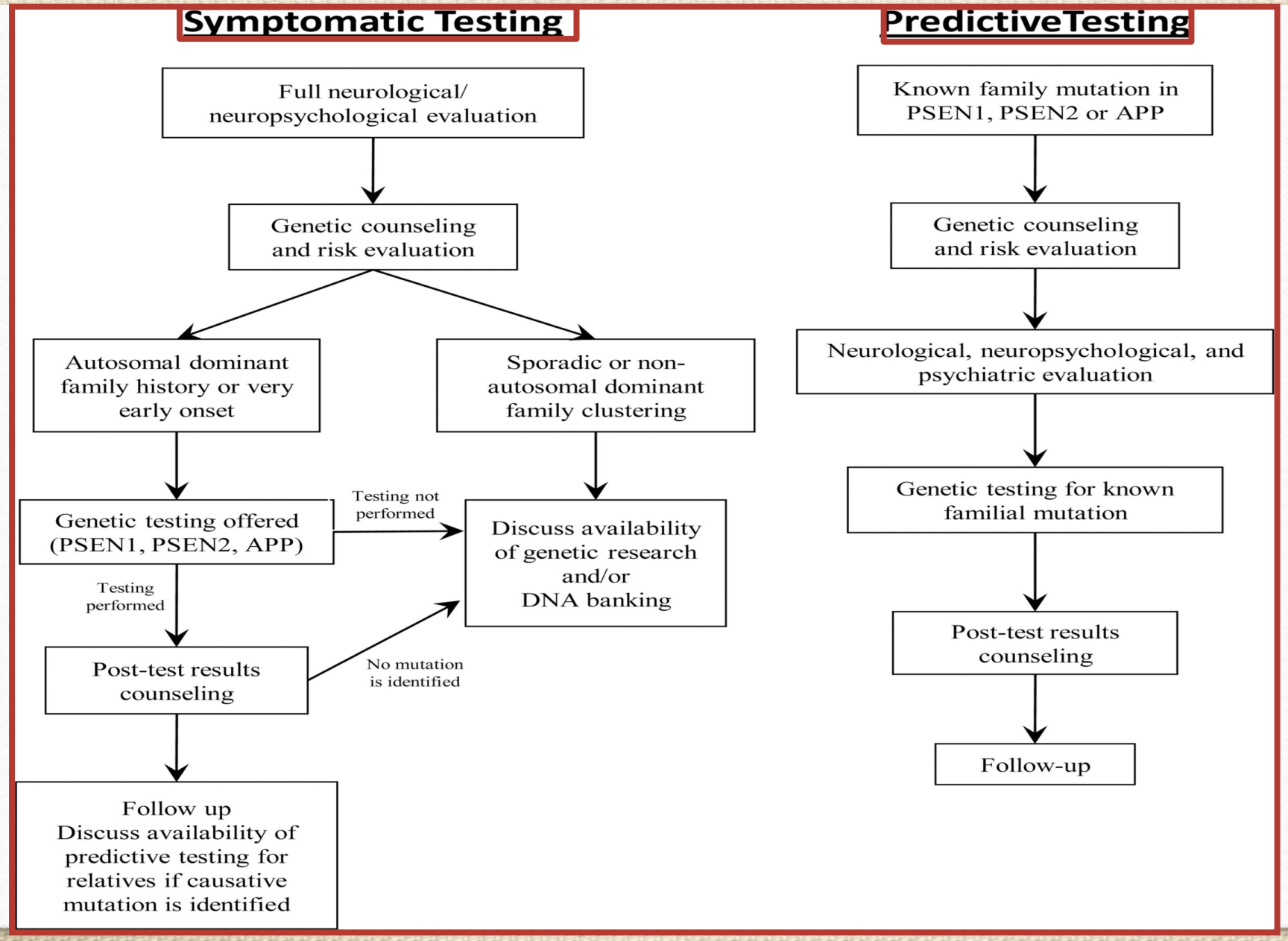
In persons who meet the core clinical criteria for probable AD dementia, evidence of a causative genetic mutation (in *APP, PSEN1, or PSEN2*), increases the certainty that the condition is caused by AD pathology. The workgroup noted that carriage of the ε4 allele of the apolipoprotein E gene was not sufficiently specific [20] to be considered in this category.

Genetic counseling and testing for Alzheimer disease: Joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors

GENETIC TESTING FOR AUTOSOMAL DOMINANT AD IN ADULTS

The use of genetic testing for diagnostic purposes in early-onset autosomal dominant AD has long been debated by clinicians in the dementia field.[50,86,87] Although mutations are rare and testing may reveal variants of unknown significance, genetic testing may result in definitive diagnosis, improve understanding for the family, and allow at-risk relatives to have the option of predictive testing.[88,89] Genetic counseling for symptomatic patients should be performed in the presence of the individual's legal guardian or family member to help assess the level to which he/she is able to understand the purpose and possible results of the genetic test and to provide informed consent (Fig. 1).[90]

Goldman et al *Genetics IN Medicine* • Volume 13, Number 6, June 2011



Genetic counseling and testing for Alzheimer disease: Joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors

Goldman J et al Genet med 2011

Guidelines

Goldman J et al Genet Med 2011

Genetic counseling and testing for Alzheimer disease: Joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors

Pediatric testing for AD should not occur. Prenatal testing for AD is not advised if the patient intends to continue a pregnancy with a mutation.

Genetic testing for AD should only occur in the context of genetic counseling (in-person or through videoconference) and support by someone with expertise in this area.

Symptomatic patients: Genetic counseling for symptomatic patients should be performed in the presence of the individual's legal guardian or family member.

A ≥3-generation family history should be obtained, with specific attention to the age of onset of any neurologic and/or psychiatric symptoms, type of dementia and method of diagnosis, current ages, or ages at death (especially unaffected relatives), and causes of death. Medical records should be used to confirm AD diagnosis when feasible. The history of additional relatives may prove useful, especially in small families or those with a preponderance of early death that may mask a history of dementia.

A risk assessment should be performed by pedigree analysis to determine whether the family history is consistent with EOAD or LOAD and with autosomal dominant (with or without complete penetrance), familial, or sporadic inheritance.

CLINICAL PRACTICE GUIDELINES/CONCENSUS STATEMENTS

Recommendations of the 4th Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDTD4)

Serge Gauthier, MD, Christopher Patterson, MD, Howard Chertkow, MD, Michael Gordon, MD, Nathan Herrmann, MD, Kenneth Rockwood, MD, Pedro Rosa-Neto, MD, PhD, Jean-Paul Soucy, MD on behalf of the CCCDTD4 participants*

McGill Center for Studies in Aging, Montreal, QC

DOI:http://dx.doi.org/10.5770/cgj.15.49

TABLE 2.
Recommendations regarding early onset dementia

- All patients with early onset dementia should be referred to a memory clinic, preferably one with access to genetic counselling and testing when appropriate.
- The cost of genetic counselling and testing should be covered by public funding.
- Physicians should be sensitive to the special issues associated with early onset dementia, particularly in regard to loss of employment and access to support services appropriate for that age group.
- Considering the rarity of early onset dementia, a national registry for interested at-risk individuals, mutation carriers and symptomatic patients will facilitate therapeutic research.
- This registry should be supported by public funding

CANADIAN GERIATRICS JOURNAL, VOLUME 15, ISSUE 4, DECEMBER 2012

Genetic tests for Alzheimer's disease Alzheimer’s society, 2013

The use of genetic testing for diagnosing early-onset Alzheimer's disease has long been debated by clinicians in the dementia field. Two authorities — the American College of Medical Genetics and the National Society of Genetic Counselors — now have published guidelines that say testing, even where marginally appropriate, shouldn't be done without expert counseling. They caution the testing is of little use, and add:

- • Children should not be tested for Alzheimer's.
- • Genetic testing should occur only with genetic counseling and support by an expert.
- • People should not use direct-to-consumer testing.
- • Patients should be informed that there currently are no proven medications or lifestyle choices that reduce the risk of developing Alzheimer's or stop its progression.
- • Patients should be told that the risk of Alzheimer's is 10 to 12 percent across a lifetime of 75 to 80 years; the effects of ethnicity are still unclear; and although some risk genes are known, there are very likely others researchers don't yet know about.

Genetic counseling

Processo attraverso cui i pazienti o i loro familiari, a rischio per una malattia ereditaria vengono informati circa la tipologia e le conseguenze della malattia, le probabilità di svilupparla e trasmetterla e le opzioni per effettuare una gestione e una pianificazione familiare.

L'informazione corretta è indispensabile perché il soggetto possa prendere una decisione e ha molte ricadute.

Decidere di *SAPERE* vale quanto decidere di *NON SAPERE* e va rispettato.

Se la demenza è genetica non è più solo un affare di famiglia ma di «famiglie».

E' un problema etico ma la consapevolezza può aiutare a trasformare l' inevitabile sofferenza della malattia in una speranza di miglioramento per le generazioni future.

Vantaggi Potenziali /PROS

I test genetici predittivi offrono ai soggetti a rischio presintomatici la possibilità di definire il rischio personale così permettendo la pianificazione della propria vita, la possibilità di decisioni e scelte comprese quelle relative alla vita riproduttiva

Sottoporsi al test predittivo può aiutare gli individui a rischio a gestire meglio i sentimenti riguardo il loro stato, riducendo appunto l' incertezza e consentendo una pianificazione futura

Gooding HC et al In Patient Educ Couns 2013; Bruni AC et al 2014 ADAD

Timori e Preoccupazioni /CONS

- Un test genetico positivo può scatenare una risposte psicologiche negative, depressione severa, ansia, mancanza di speranza e anche ideazioni suicidarie.
- Da un punto di vista sociale/legale, la persona potrebbe essere oggetto di potenziale discriminazione genetica per esempio nel trovare un lavoro, o comunque nell'ambiente di lavoro per la carriera, ancora si potrebbero ravvisare problemi assicurativi o ancora nella creazione di relazioni.

Tiben et al 1997 J Med Genet;
Goldman et al 2011 Genet Med

Protocollo Armonizzato di Consulenza Genetica ItalianDIAfN

Definizione del protocollo

Journal of Alzheimer's Disease 51 (2016) 277–291
DOI 10.3233/JAD-150849
IOS Press

Genetic Counseling and Testing for Alzheimer's Disease and Frontotemporal Lobar Degeneration: An Italian Consensus Protocol

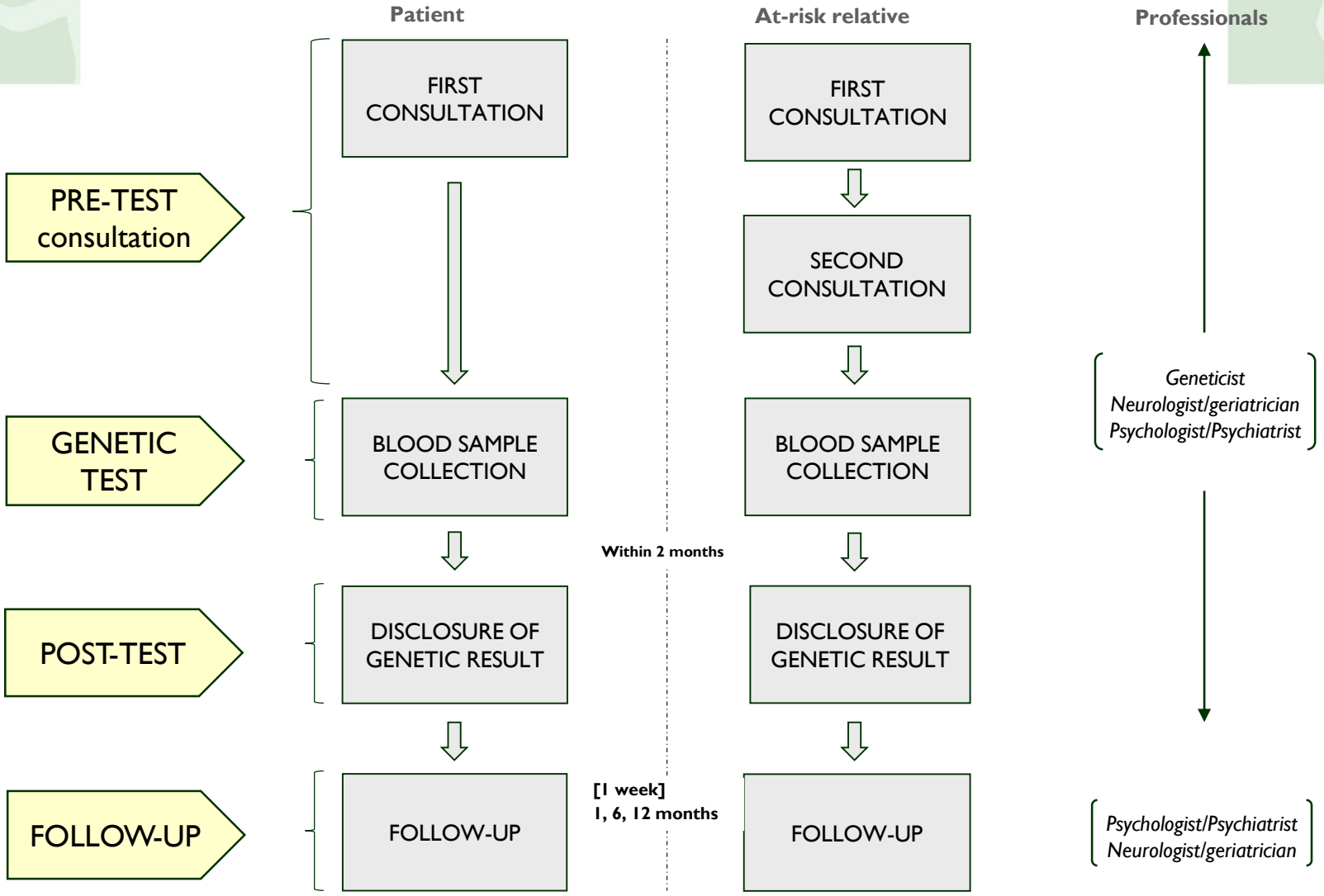
Martina Bocchetta[a,b], Anna Mega[a], Livia Bernardi[c], Emilio Di Maria[d], Luisa Benussi[e], Giuliano Binetti[f], Barbara Borroni[g], Rosanna Colao[c], Giuseppe Di Fede[h], Silvia Fostinelli[e], Daniela Galimberti[i], Massimo Gennarelli[j], Roberta Ghidoni[e], Irene Piaceri[k], Michela Pievani[a], Corinna Porteri[l], Veronica Redaelli[h], Giacomina Rossi[h], Silvia Suardi[h], Claudio Babiloni[m], Elio Scarpini[i], Fabrizio Tagliavini[h], Alessandro Padovani[g], Benedetta Nacmias[k], Sandro Sorbi[k], Giovanni B. Frisoni[a,n], SINdem[‡], Amalia C. Bruni[c,*]

[‡]SINdem Collaborators:

Marco Bozzali[o], Lucilla Parnetti[p], Carlo Ferrarese[q], Stefano F. Cappa[r], Camillo Marra[s], Carlo Masullo[t], Innocenzo Rainero[u], Vincenzo Silani[v], Giuseppe Sorrentino[w], Giuseppe Bruno[x], Annachiara Cagnin[y]

ItalianDIAfN genetic counseling protocol

Procedure for patient and at-risk relative

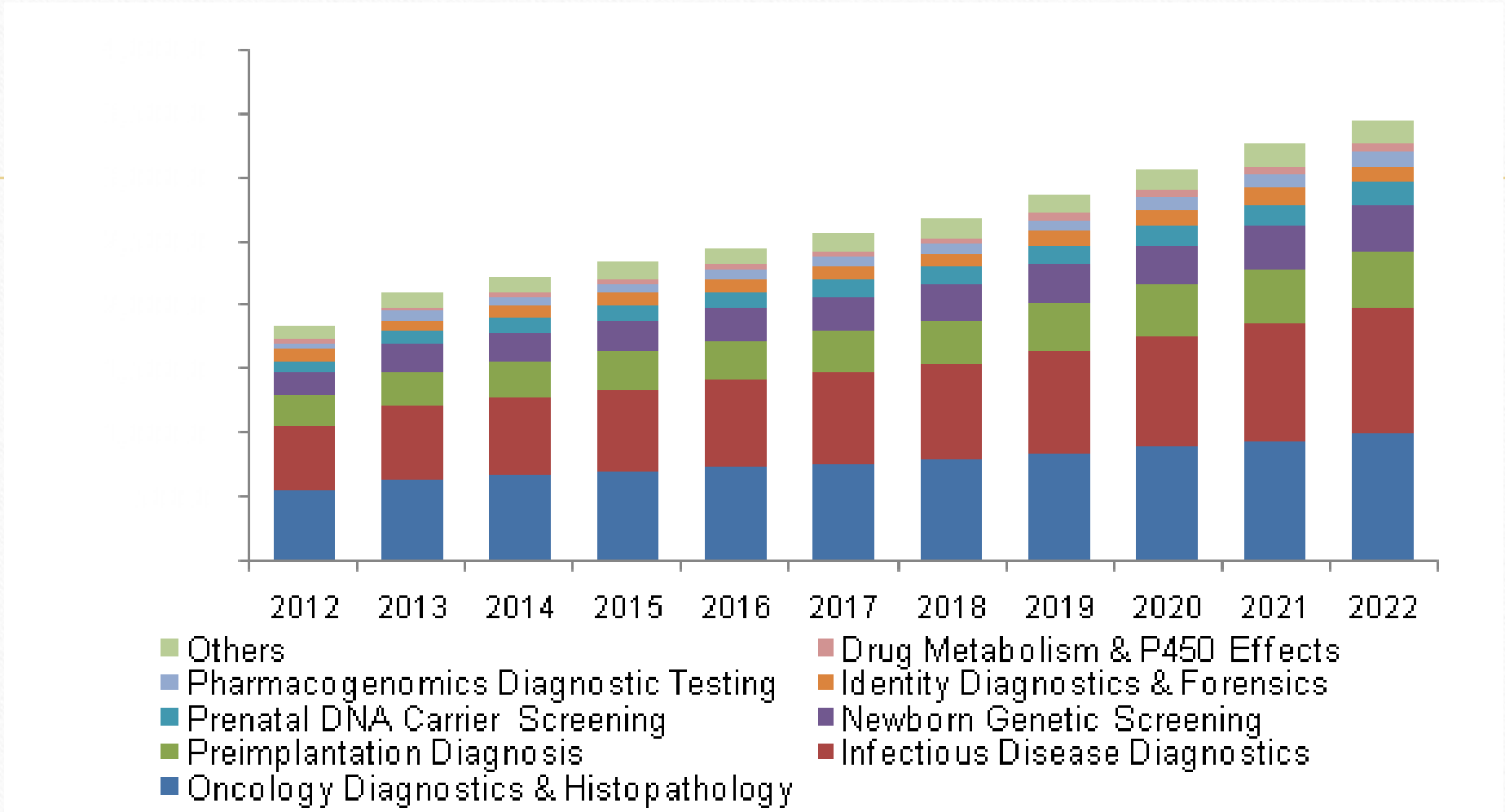


Bocchetta M et al. Genetic Counselling and testing for Alzheimer's Disease and Frontotemporal Lobar Degeneration: an Italian Consensus Protocol. *Journal of Alzheimer's Disease 2016;51(1):277-91*

TEST	Descrizione
BFQ- Big Five Questionnaire	Tests di personalità
SF-12	Questionario sullo stato di salute
WHOQOL	Test per la valutazione della qualità della vita
STAI-Y (State Trait Anxiety Inventory)	Test per la misurazione dell'ansia
BDI (Beck Depression Inventory)	Questionario per la valutazione della depressione
HRSD (Hamilton Rating Scale for Depression)	Valutazione della depressione e del rischio suicidio
BC (Brief COPE)	Valutazione dello stile di Coping
RSA (Resilience Scale for Adult)	Valutazione della Resilienza
HLC – Health Locus of Control	Valuta la capacità dell'individuo nell'individuare una relazione causale tra le proprie azioni e le relative conseguenze

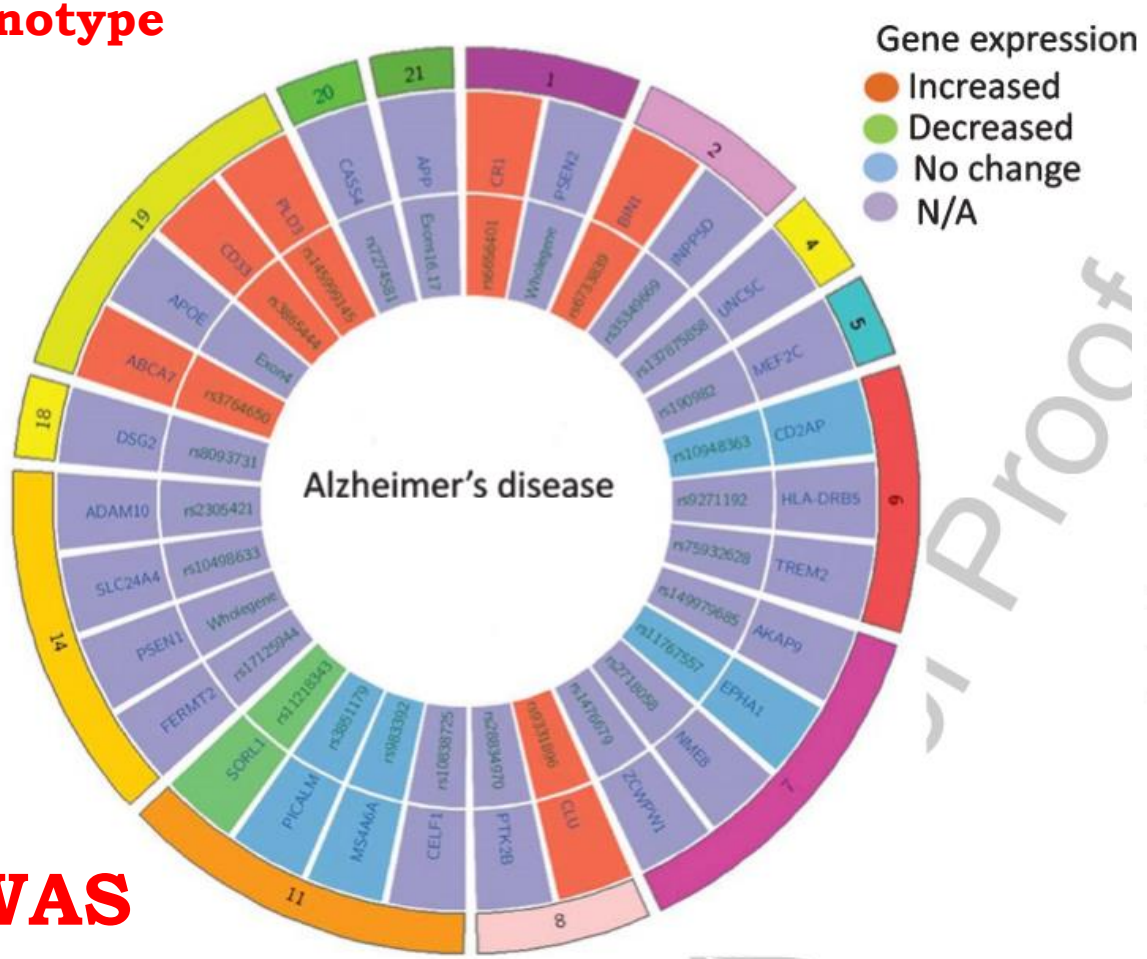
Cosa sta ancora succedendo???

Esponenziale offerta su internet di test a basso costo senza alcun processo di «protezione» per il soggetto



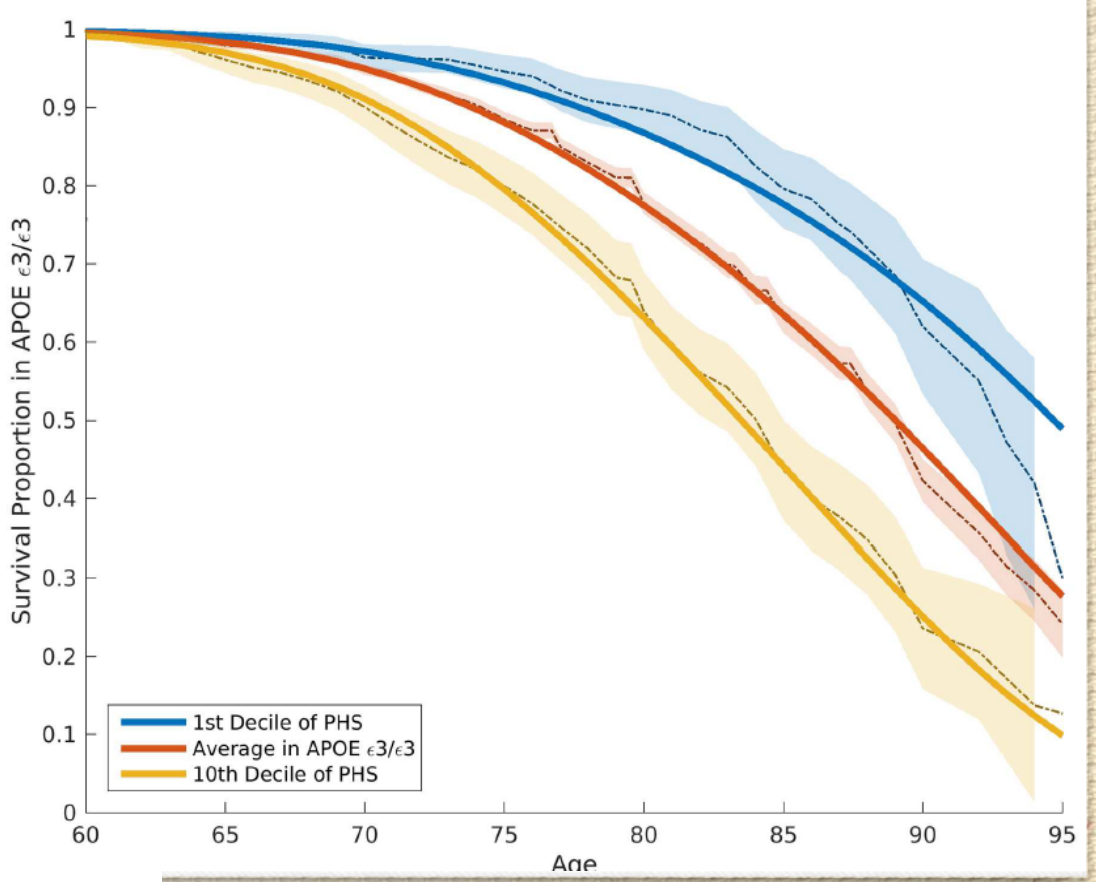
Identificazione di enormi quantità di polimorfismi (sia di rischio che di protezione) che necessitano di conoscenze molto approfondite per poter essere comunicate

Common variants with small effect
Increasing decreasing risk or modulating phenotype



GWAS

Polygenic hazard score in E3E3



Zhu et al JAD 2017 DOI 10.3233/JAD-170062

Desikan RS, Fan CC, Wang Y, Schork AJ, Cabral HJ, Cupples LA, et al. (2017) PLoS Med 14(3): e1002258. doi:10.1371/journal.pmed.1002258

Possibilità di partecipare a clinical trials innovativi che hanno come obiettivo il trattamento farmacologico di demenze genetiche

Alzheimer's prevention trials

RCT	Participants	Treatment	Outcome measures
API: Alzheimer's Prevention Initiative	300 members of Colombian families, (200 carriers of a mutated *PSEN1* gene) Age: 30+ y	Crenezumab (Genentech) Duration: 5 y	Primary: Cognitive. Secondary: Biomarkers, including brain scans to measure amyloid load and brain atrophy
DIAN: Dominantly Inherited Alzheimer Network USA, Australia, UK	240 members of families with early-onset AD; 60 have a mutation in one of three genes (*PSEN1, PSE2, APP*) Age: NA	Three antiamyloid therapies to be determined Duration: 2 years + extension	An initial phase will use biomarkers to identify the most promising drug candidate for a follow-up phase to examine cognitive effects
A4: Anti-Amyloid Treatment of Asymptomatic AD	1500 healthy seniors, including 500 with amyloid positive brain scans Age: 70+ y	One antiamyloid therapy to be determined Duration: 3 years	Primary: Cognitive Secondary: Biomarkers

Identificazione di mutazioni genetiche anche in casi sporadici

PERSPECTIVE

Don't keep it in the family

Let's start describing ALS on the basis of its cause, not on whether someone obtained a relevant family history, says **Ammar Al-Chalabi**.

The terms familial ALS and sporadic ALS are outdated and illogical. They impede research, confuse patients and cloud our thinking. It's time to ditch them.

A major goal of research into amyotrophic lateral sclerosis (ALS) is the discovery of its causes. The idea is that understanding the genetic (often equated with familial) and environmental (often equated with sporadic) factors leading to ALS will give insights that will help to design new treatments. If we discard for a moment the implicit assumption that the causes of ALS are the same as the processes that perpetuate it, there remains a major flaw in this way of thinking. We are taught that 5–10% of ALS is familial and the remainder sporadic. This false distinction affects the design and interpretation of research. For example, sporadic ALS is considered synonymous with ALS not associated with a Mendelian disease gene, whereas this is not necessarily the case. Or a mutation may be described as causing familial ALS, even though mutations in every gene that's been linked to the condition have also been found in people with apparently sporadic ALS[1]. The muddy nomenclature affects the way the disease is managed in the clinic and the information given to patients; genetic counselling, for example, is usually reserved for those with a family history.

The terms familial and sporadic are not useful for several reasons. First, neurologists have wildly varying definitions of familiality. Take a situation in which a woman, her father and uncle all have ALS. That would strike many people as a textbook example of familial ALS, but not everyone would agree with that classification. On the other hand, there are experts who consider that a situation in which the only affected individuals of a family are fourth cousins is

IT IS ARBITRARY TO SAY THAT A FAMILY WITH ONE AFFECTED PERSON SHOULD BE REGARDED AS DIFFERENT FROM A FAMILY WITH MORE THAN ONE.

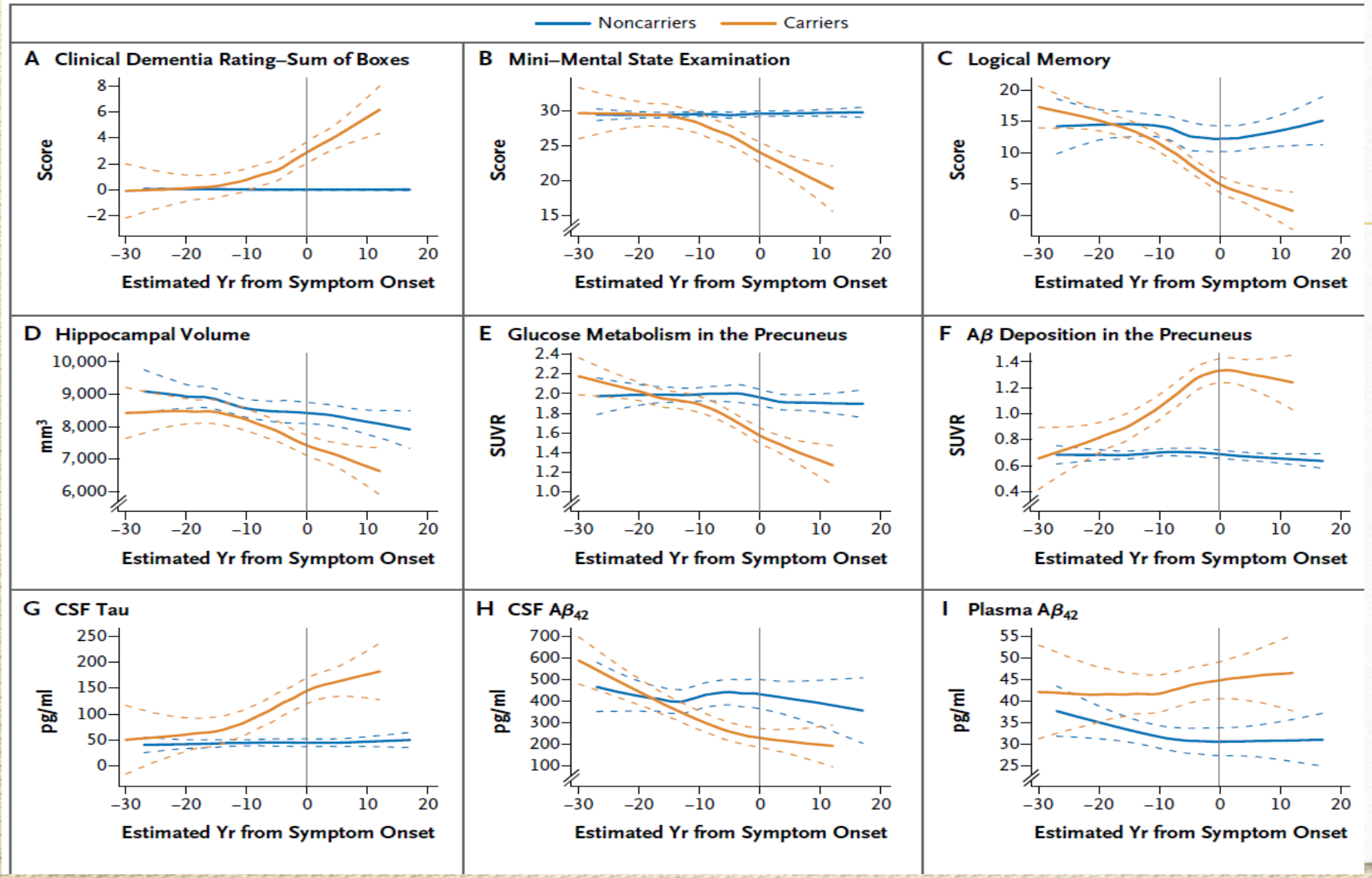
disease-gene variant, the pattern of inheritance will frequently be classified as sporadic[5]. This is due to two factors. First, not every person who inherits a disease-causing mutation will manifest the disease. Second, the probability of transmission is 50% per child, so in smaller families there are fewer opportunities for a mutation to be transmitted. Therefore, it is arbitrary to say that a family with one affected person should be regarded as meaningfully different from a family with more than one.

Evidence has emerged suggesting that the development of ALS may be a multistep process in which, on average, six molecular steps must occur, similar to some types of cancer[6]. In this situation, a genetic variant conferring a large risk would be expected to account for several of the steps, explaining the higher probability of disease in a mutation carrier. That means that it makes sense to search for environmental risk factors in those with a clear genetic basis to their ALS, because there will be only one or two factors left to identify. This is true regardless of family history.

It is easy to demonstrate the harmful consequences of the archaic familial/sporadic division. Let us take the most frequent cause of ALS: expansion mutation in the gene *C9ORF72*. This is present in about 45% of people with a family history, making it by far the most important cause of 'familial' ALS. But this mutation is also present in up to 10% of the much larger number of people with apparently no relevant family history, so it is the most important cause of 'sporadic' ALS as well. In fact, these mutations account for about 14% of all ALS, and in most cases there will be no family history. How can it make sense to treat people differently on the basis of their family history in this context?

Genetic Tests should be offered regardless of family history and genetic counselling should be offered to all ALS patients

Maggiore consapevolezza dei soggetti a rischio con aumento delle richieste



DIAN
Dominantly Inherited Alzheimer Network

DIAN Bateman et al NEJM 2013

Conclusioni

- Le applicazioni all'uomo delle potenzialità derivate dalla ricerca genetica pongono problemi etici che coinvolgono non solo il singolo ma l'intera società. L'evoluzione delle conoscenze teoriche e delle tecnologie applicate al genoma hanno offerto opportunità ma anche sollevato problemi che non hanno precedenti nella storia dell'uomo.
- La ricerca e il progresso sono valori fondamentali, specialmente se finalizzati alla salute, e se i relativi problemi etici sono affrontati nelle sedi opportune, con dibattiti multidisciplinari e pluralistici. Allo scopo di garantire che le ricadute delle ricerche siano vantaggiose per l'uomo, è necessario che siano rispettati alcuni principi fondamentali, come il diritto all'informazione, la libertà di scelta, il rispetto della dignità e della vita d'ogni persona, il rispetto per le convinzioni personali e religiose, la riservatezza dei dati, il raggiungimento dell'equità per ciascuno.
- Solo su una base di valori forti e condivisi potranno essere costruite regole di comportamento giuste ed efficaci per tutti

Conclusioni

- La conoscenza delle cause genetiche delle malattie neurodegenerative autosomico dominanti non si è evoluta ancora in parallelo allo sviluppo di farmaci efficaci né per la cura, né per la prevenzione delle stesse.
- E' innegabile tuttavia che, nonostante la mancanza di terapie curative e preventive, al consultando che lo richiede, il test presintomatico porti una serie di documentati benefici.
- In particolare, la fine di un sentimento di incertezza difficile da gestire a lungo e la possibilità di pianificare sia la vita familiare che le scelte riproduttive in funzione della conoscenza ottenuta .

(Codori 1997;Taylor and Myers 1997; Dufrasne et al., 2010).


QUANDO PENSI DI AVERE TUTTE LE RISPOSTE, LA VITA TI CAMBIA TUTTE LE DOMANDE..

Grazie!!!