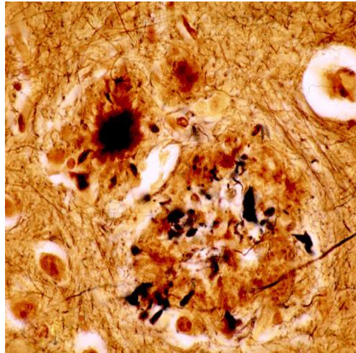
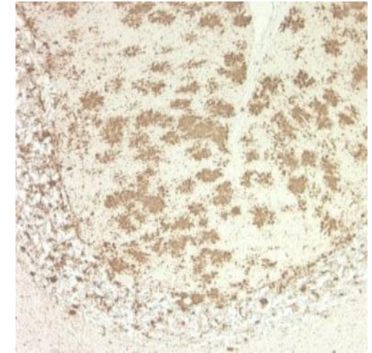
COMMONALITY IN THE CLINICAL APPROACH TO ADRD & PRION DISEASE





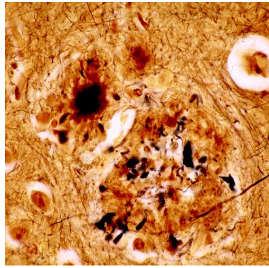
Richard Knight

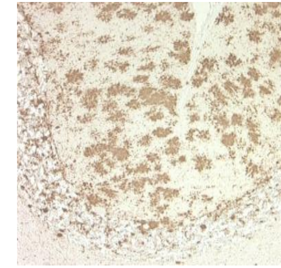
NCJDRSU

Centre for Clinical Brain Sciences

University of Edinburgh

COMMONALITY IN THE CLINICAL APPROACH TO ADRD & PRION DISEASE





INTRODUCTORY REMARKS

DIAGNOSIS

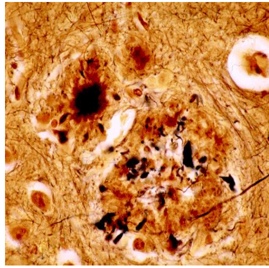
MANAGEMENT

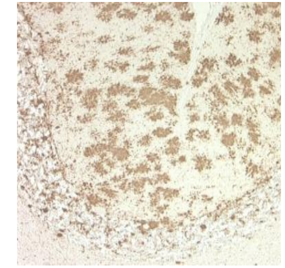
TREATMENT

DIFFERENCES ?

CONCLUDING REMARKS

COMMONALITY IN THE CLINICAL APPROACH TO ADRD & PRION DISEASE





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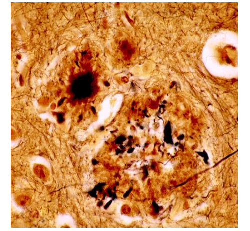
NEURODEGENERATIVE DISEASES



PROGRESSIVE NEUROLOGICAL IMPAIRMENT

DUE TO

NEURONAL DYSFUNCTION & LOSS

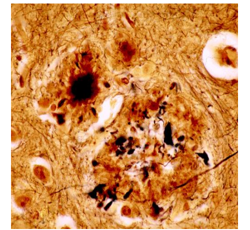
ASSOCIATED WITH

MIS-FOLDING OF ONE OR MORE PROTEINS

DEPOSITION OF AGGREGATES OF THESE PROTEINS IN NEURAL TISSUE

THE PRECISE CAUSE OF NEURONAL DYSFUNCTION/DEATH IS OFTEN NOT CLEAR

NEURODEGENERATIVE DISEASES



TYPICALLY

BEGINNING IN SPECIFIC AREAS / CELL-TYPES OF THE CNS
PROGRESSING TO MORE GLOBAL INVOLVEMENT

AGE-RELATED

SPORADIC & GENETIC FORMS

NEURODEGENERATIVE DISEASES

‘COGNITIVE’ GROUP

AD

FTD

LBD

VCID

CJD

‘MOTOR’ GROUP

PD

ALS

HD

MSA

NEURODEGENERATIVE DISEASES

'COGNITIVE' GROUP

AD

FTD

LBD

VCI

CJD

'MOTOR' GROUP

PD

ALS

HD

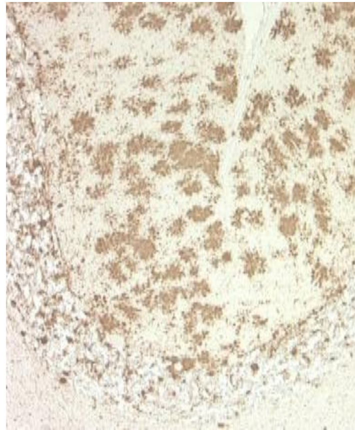
MSA

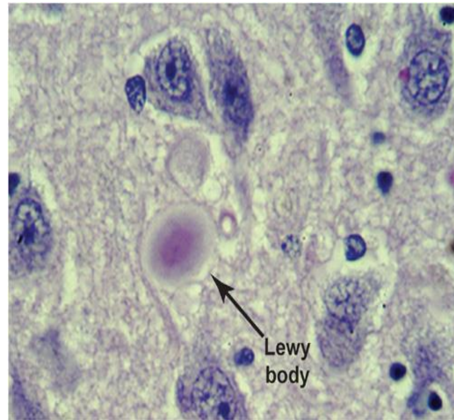
1980: in the fold

CJD

2024: back in the fold

NATURE'S MESSAGE SEEMS INCREASINGLY CLEAR

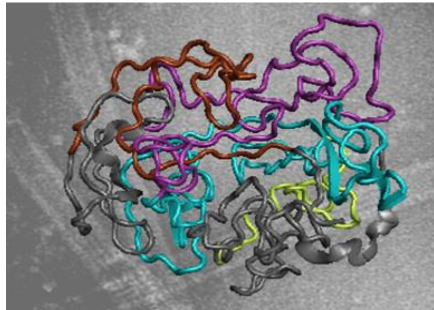


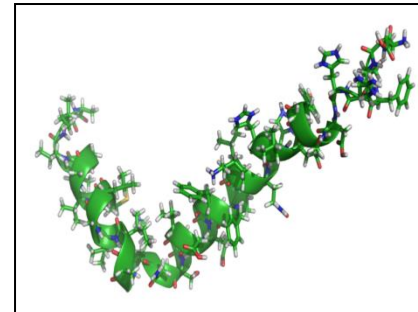


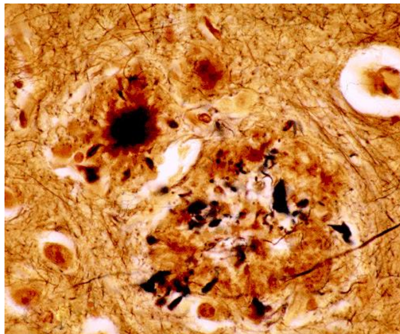
COMMON DISEASE MECHANISMS

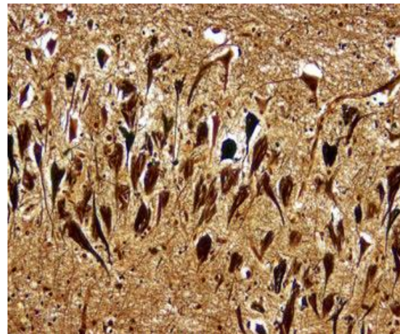
CO-OCCURRENCE OF PATHOLOGIES IN ONE BRAIN

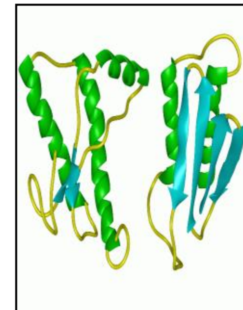
INCREASING EVIDENCE OF PROTEIN INTERACTIONS

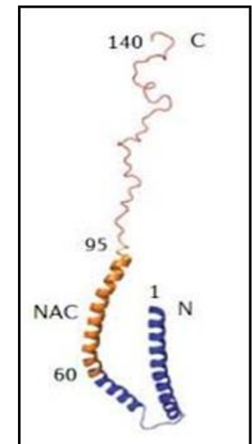












UK NCJDRSU
PATHOLOGY FINDINGS
123 cases of Definite CJD

CONFIRMED CJD CASES

CO-PATHOLOGY FOUND: 50%

CORRELATION WITH AGE

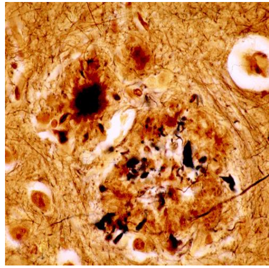
Most Common:

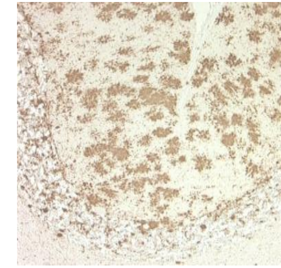
CAA	26%
AD	13%
LBD	9%

A Broader View of dementia: multiple co-pathologies are the norm
Coulthard & Love
Brain 2018

"Perhaps we should aim to classify patients clinically according to their spectrum of pathological change, rather than trying to fit them into eponymous syndromes."

COMMONALITY IN THE CLINICAL APPROACH TO ADRD & PRION DISEASE





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THE GENERAL DIAGNOSTIC PROCESS
COMMON TO ALL DISEASES

ASSESS THE CLINICAL PICTURE

DIFFERENTIAL DIAGNOSIS

TIME & TESTS

FINAL DIAGNOSIS

THE GENERAL DIAGNOSTIC PROCESS

COMMON TO ALL DISEASES

ASSESS THE CLINICAL PICTURE

ASSESS THE CLINICAL PICTURE

PrD & ADRD: MANY COMMON ELEMENTS

MOSTLY MIDDLE AGED-ELDERLY

FH IMPORTANT

COGNITIVE & ‘PSYCHIATRIC’ FEATURES

ASSESS THE CLINICAL PICTURE

PrD & ADRD: MANY COMMON ELEMENTS

MOSTLY MIDDLE AGED-ELDERLY

FH IMPORTANT

COGNITIVE & 'PSYCHIATRIC' FEATURES

OTHER FEATURES

Visual Impairments

Motor Impairments

Involuntary Movements

ASSESS THE CLINICAL PICTURE

PrD & ADRD: *INITIAL PRESENTATIONS OFTEN NON-SPECIFIC*

Forgetfulness

Confusion

Mood / Personality Change

Language impairment

Visuo-Spatial Perception Impairment

Motor impairments

Involuntary movements

ASSESS THE CLINICAL PICTURE

PrD & ADRD: REQUIRES COMMON CLINICAL SKILLS

UNDERSTANDING OF:

COGNITIVE IMPAIRMENT

PSYCHIATRIC SYMPTOMS

COMPETENCE IN:

COGNITIVE/NEUROLOGICAL HISTORY TAKING

THE PHYSICAL NEUROLOGICAL EXAMINATION

COMMONALITY OF SKILLS ARGUES FOR COMMONALITY OF SERVICE

A COGNITIVE SERVICE

RUN BY CLINICIANS WITH EXPERIENCE IN

ALL NEURODEGENERATIVE DISORDERS

&

THEIR DIFFERENTIAL DIAGNOSES

RISK OF OVER-SPECIALISATION
Lessons from Stroke ?

Any acute brain syndrome: TIA or Stroke ?

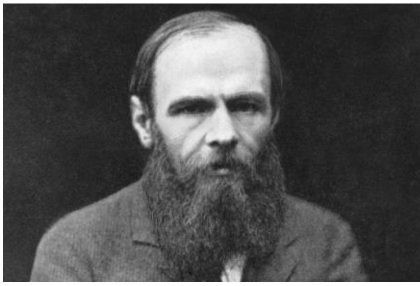
The UK:

Increasingly seen by Stroke Physicians

With relatively little general neurology experience

In a proportion:

Other conditions mis-diagnosed as TIA or Stroke



The Brothers Karamazov
Dostoevsky 1879-1880

The old-fashioned doctor…has completely disappeared, now there are only specialists.

If your nose hurts, they send you to.. a specialist..

”I can treat only your right nostril”, he says, “I don't treat left nostrils, it's not my specialty, but there's a separate specialist..who will finish treating your left nostril.”

THE GENERAL DIAGNOSTIC PROCESS
COMMON TO ALL DISEASES

DIFFERENTIAL DIAGNOSIS

NATIONAL REFERRAL SYSTEM FOR SUSPECTED PRION DISEASE UK

Since 1990

Clinicians refer all cases of ‘suspected CJD’

[phone or email]

Referrals: ~1/4 have prion disease

NATIONAL REFERRAL SYSTEM FOR SUSPECTED PRION DISEASE UK

Referrals: ~1/4 have prion disease

Reasons for referral as ‘suspected CJD’

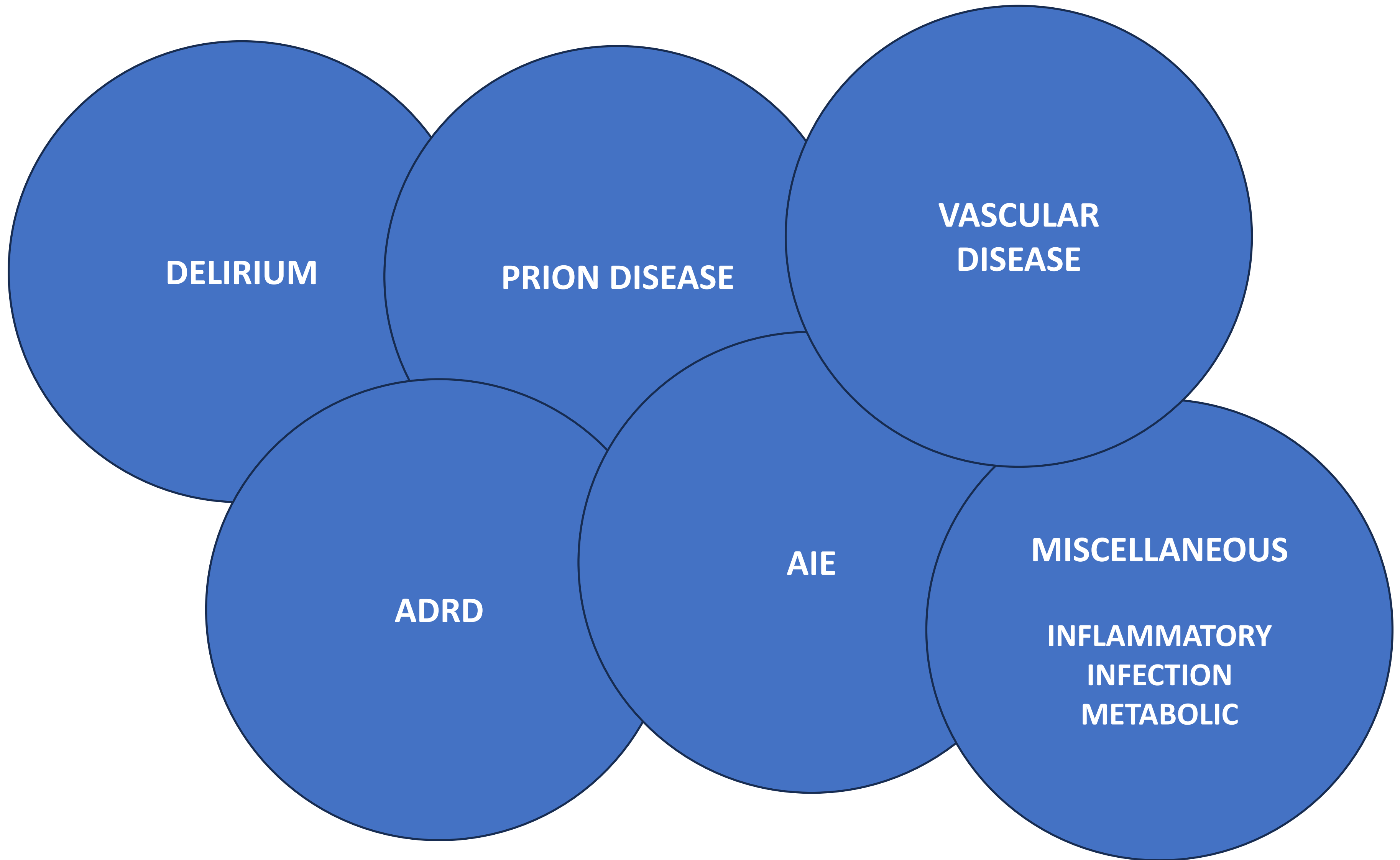
‘Rapid’ Progression

Normal ‘routine’ tests

MR brain findings

Myoclonus

COMMONALITY IN DIFFERENTIAL DIAGNOSES



UK SURVEILLANCE:

THE LAST 23 SUSPECT CASES WITH DEFINITE ALTERNATIVE DIAGNOSES

LBD / AD / LBD+AD	7	
VCID	5	
CBD	2	61% ADRD
MND	1	
INFLAMMATORY / IMMUNE	5	
METABOLIC	2	
PRIMARY PSYCHIATRIC	1	

SOME SELECTED PUBLISHED DATA

Geschwind et al	2009	San Francisco	RPD: 15-20% not CJD 26% of not CJD: Neurodegenerative
Bentivenga et al	2024	Bologna	N-Path of RPD 22 rpDLB & 31 rpAD cases
Haik et al	2000	France	N-Path of RPD. 117/465 Not CJD AD & DLB Commonest N-Degen
Tschampa et al	2001	Germany	Suspected CJD Autopsy: 19 AD, 12 DLB

Common Themes

DURATION

sCJD <6m 60% but 15% >12m

LBD & AD slower but rpLBD & rpAD recognized

CLINICAL FEATURES

Myoclonus not uncommon In DLB & AD

ASSESS THE CLINICAL PICTURE

PrD & ADRD: REQUIRES COMMON CLINICAL SKILLS

UNDERSTANDING OF:

THE PARTICULAR

HISTORY & EXAMINATION ASPECTS

THAT HELP TO DIFFERENTIATE

DIFFERENT POSSIBLE DIAGNOSES

THE GENERAL DIAGNOSTIC PROCESS

COMMON TO ALL DISEASES

TIME & TESTS

THE CLINICAL PROCESS IS PHASED

INITIAL CLINICAL PHASE FOCUS:
MOSTLY *NON-NEURODEGENERATIVE & POTENTIALLY TREATABLE* CAUSES

‘ROUTINE’ BLOOD TESTS

BRAIN MR

BRAIN CT

‘ROUTINE’ CSF

THE CLINICAL PROCESS IS PHASED

LATER CLINICAL PHASE FOCUS:
***SPECIFIC NEURODEGENERATIVE* DIAGNOSES**

BRAIN MR

OTHER TESTS

CONVERGENCE OF APPROACH: SPECIFIC-IN-PRINCIPLE TESTS

DETECTION OF RELEVANT ABNORMAL PROTEIN
IDENTIFICATION OF SPECIFIC GENETIC MUTATION

TIME AS A DIAGNOSTIC PROCESS

ONE DIFFERENTIATING PROCESS:

THE CLINICAL PICTURE OVER TIME

PROGRESSION

RATE OF PROGRESSION

EMERGENCE OF OTHER FEATURES

THE GENERAL DIAGNOSTIC PROCESS
COMMON TO ALL DISEASES

FINAL DIAGNOSIS

CLINICAL EXPERTISE ?

WON’T ALGORITHMS INVOLVING

DIAGNOSTIC CRITERIA & SPECIFIC TESTS

SOLVE EVERYTHING ?

DIAGNOSTIC CRITERIA ?

DIAGNOSTIC CRITERIA OFTEN DESIGNED FOR SPECIFIC PURPOSES

[not necessarily for routine clinical diagnosis]

DIAGNOSTIC CRITERIA ?

HAVING A GOOD RECIPE DOESN'T MAKE YOU A GOOD COOK

CRITERIA NEED TO BE APPLIED IN REAL CONTEXTS

SOME SUBJECTIVITY IN JUDGING IF THEY ARE MET

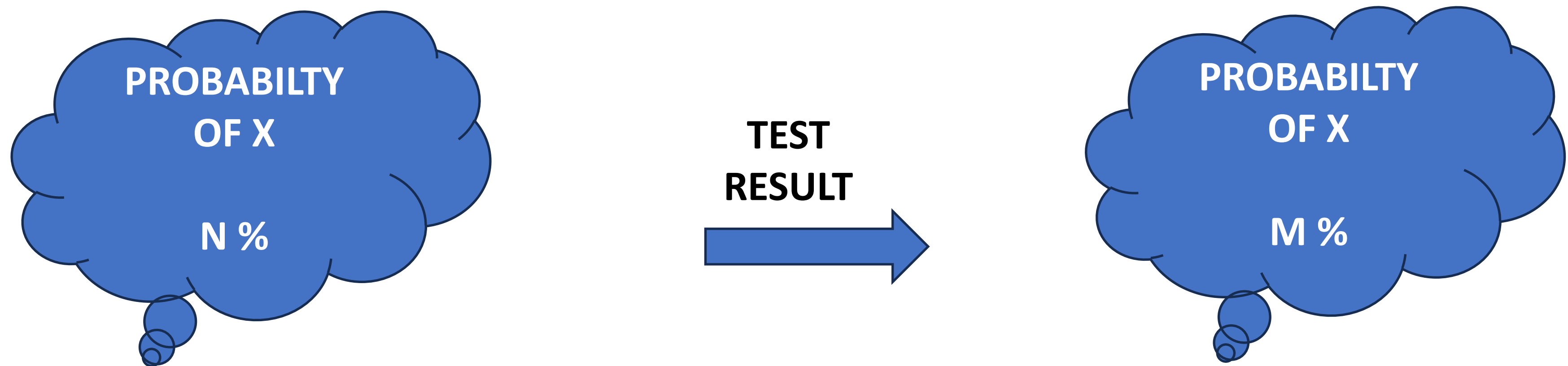
DIFFICULT TO DEVISE CRITERIA THAT COVER ALL CASES

REAL CLINICAL JUDGEMENT BASED ON EXPERIENCE NECESSARY

SPECIFIC TESTS ?

TESTS ARE NOT 'DIAGNOSTIC'

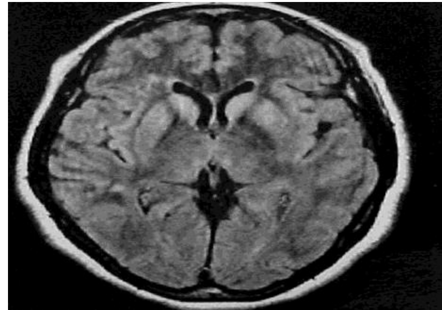
DIAGNOSIS: PERFORMED BY A *DOCTOR*

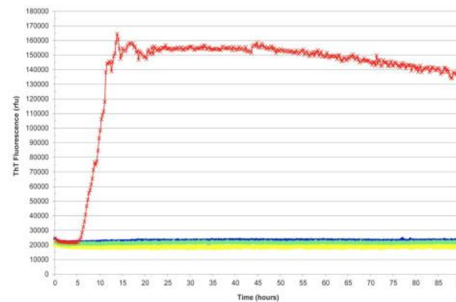


ALL TESTS NEED TO BE REQUESTED IN AN APPROPRIATE CLINICAL CONTEXT
ALL TEST RESULTS NEED TO BE EVALUATED IN THE APPROPRIATE CLINICAL CONTEXT

‘DIAGNOSTIC’ TEST ?

CJD: The success of MR & RT-QuIC has had bad as well as good effects





TESTS DEVELOPED IN A LABORATORY
NEED EVALUATION IN REAL CLINICAL CONTEXTS

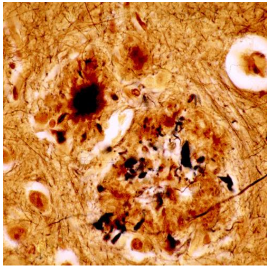
TESTS DIFFERENTIATING CJD, ADRDs & OTHERS

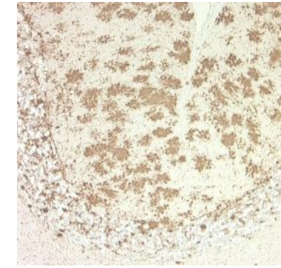
NEED TO BE ASSESSED IN MIXED CLINICAL POPULATIONS

&

CO-PATHOLOGIES MIGHT BE RELEVANT IN ASSESSMENT

COMMONALITY IN THE CLINICAL APPROACH TO ADRD & PRION DISEASE





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COMMONALITY IN
NURSING CARE
&
SYMPTOM MANAGEMENT

THE MANAGEMENT OF

CONFUSION & MEMORY IMPAIRMENT

LANGUAGE PROBLEMS

MOBILITY IMPAIRMENT

INVOLUNTARY MOVEMENTS

INCONTINENCE

FEEDING PROBLEMS

DEPENDS MOSTLY ON

THEIR NATURE & NOT THEIR CAUSE

COMMONALITY IN
GENERAL CONCERNS

CARE PLACEMENTS

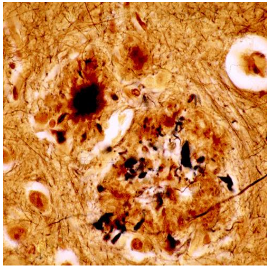
POWER OF ATTORNEY QUESTIONS

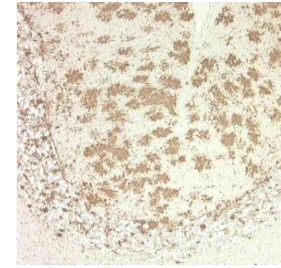
PERSONALITY CHANGES

'AMBIGUOUS LOSS'

[Pauline Boss, University of Minnesota]

COMMONALITY IN THE CLINICAL APPROACH TO ADRD & PRION DISEASE





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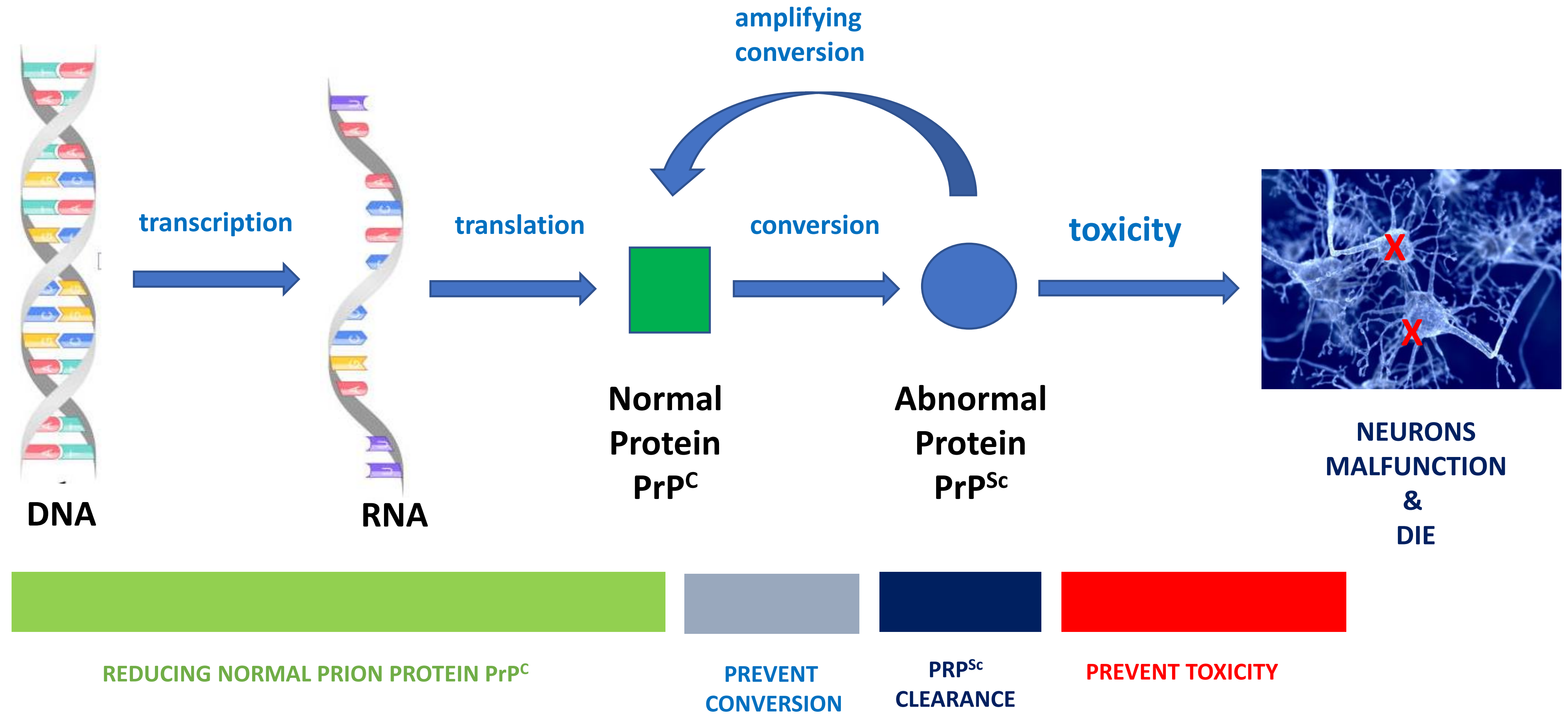
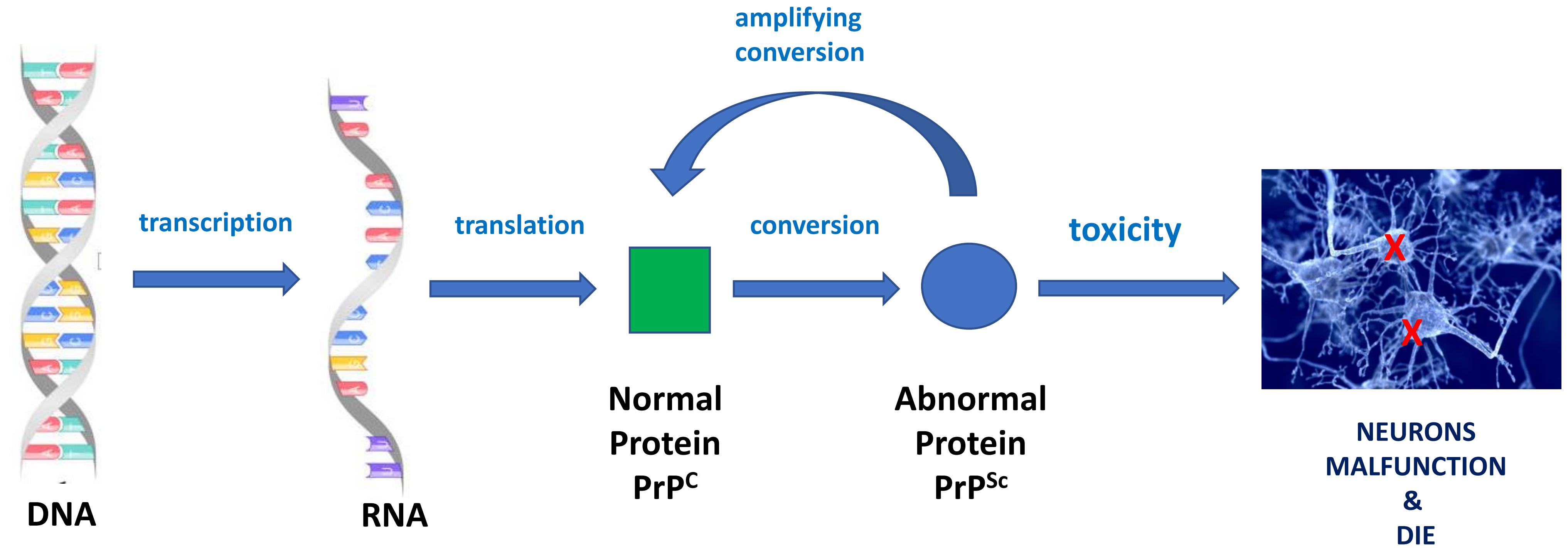
RATIONAL TREATMENT OF PRION DISEASE



RATIONAL TREATMENT OF PRION DISEASE



REDUCING NORMAL PRION PROTEIN PrP^{C}

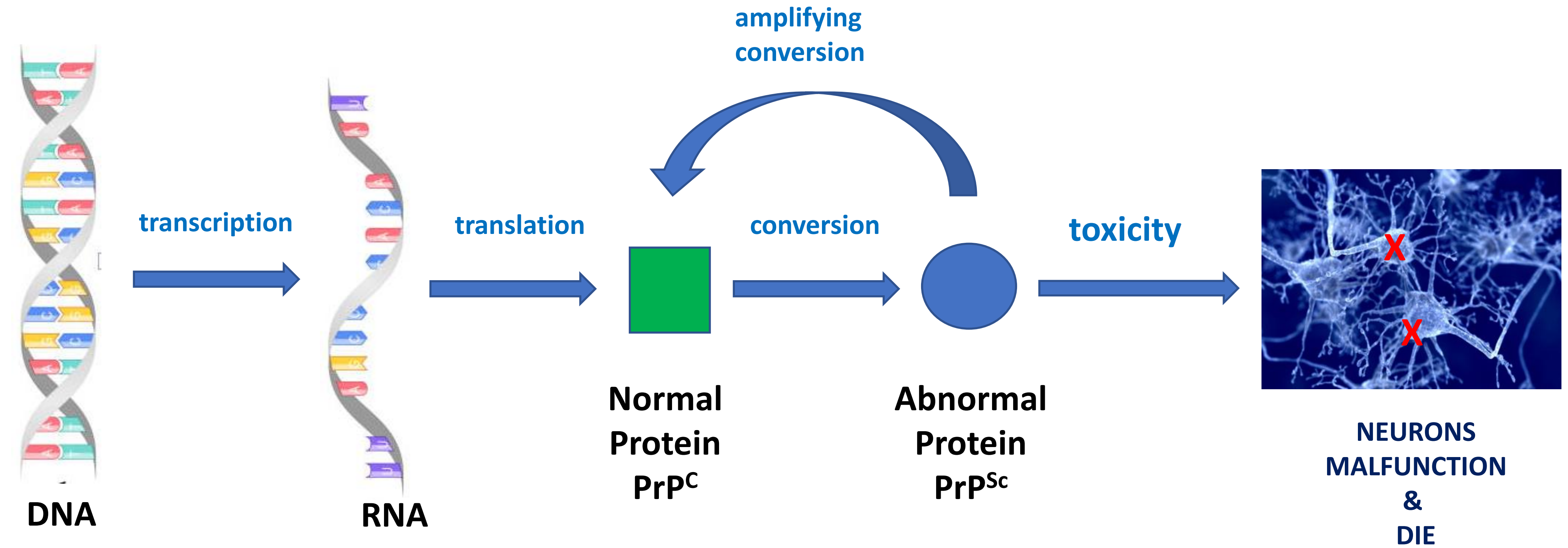
PREVENT CONVERSION

PRP^{Sc} CLEARANCE

PREVENT TOXICITY

LIKELY RELEVANCE TO OTHER PROTEIN-MISFOLDING DISEASES

RATIONAL TREATMENT OF NEURODEGENERATION



PREVENT TOXICITY

LIKELY
COMMON
TOXIC
MECHANISMS

COMMONALITY OF TREATMENT APPROACHES

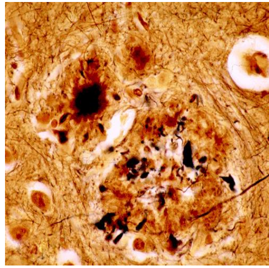
TREATMENT TRIALS & ESTABLISHED THERAPEUTICS

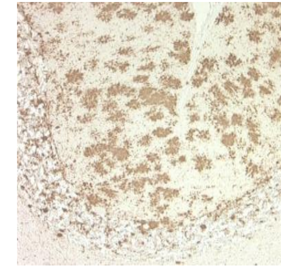
Likely to require

SIMILAR or COMMON

ASSESSMENTS & MONITORING

COMMONALITY IN THE CLINICAL APPROACH TO ADRD & PRION DISEASE





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COMMONALITY: OK
BUT DIFFERENCES ?

TIME

Rapid Progression: Different definitions of this

Elderly: may have preceding ‘forgetfulness’

COMMONALITY: OK
BUT DIFFERENCES ?

TIME

Rapid Progression: Different definitions of this

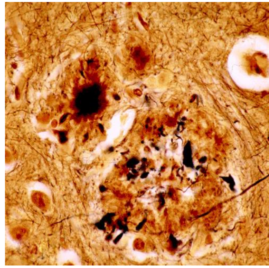
Elderly: may have preceding ‘forgetfulness’

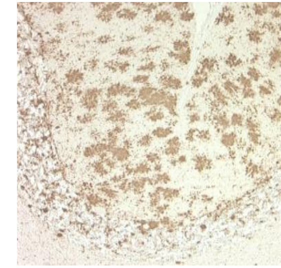
BALANCE OF ‘PHYSICAL’ & COGNITIVE

AND THEIR ORDER OF APPEARANCE

THESE ARE NOT ABSOLUTE
OVERLAPS EXIST

COMMONALITY IN THE CLINICAL APPROACH TO ADRD & PRION DISEASE





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PrD & ADRD
COMMONALITY & OVERLAP

IN

MECHANISM

CO-OCCURRENCE

CLINICAL PRESENTATION & ASSESSMENT

CARE, MANAGEMENT & TREATMENT

PrD & ADRD
REQUIRING SIMILAR OR SAME CLINICAL SKILLS

IN

CLINICAL ASSESSMENT

DIAGNOSTIC TESTS

MANAGEMENT & TREATMENT

PrD & ADRD
CONVERGENCE IN DISEASE-SPECIFIC TESTS

MODERN DIAGNOSTIC TESTS

EXTREMELY HELPFUL

But

REQUIRE & CANNOT REPLACE CLINICAL EXPERTISE

MORE POWERFUL WEAPONS REQUIRE MORE, NOT LESS, CAREFUL AIM

TECHNOLOGY IS A WONDERFUL SERVANT BUT A POOR MASTER

ADRD
CJD