Neonatal Emergencies: Rapid Genetic Diagnosis

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2003

- Completion of the 1st composite HGS

  - Precision medicine
  - Every baby will have access to WGS
  - Modify strategies for disease prevention detection and treatment

2011

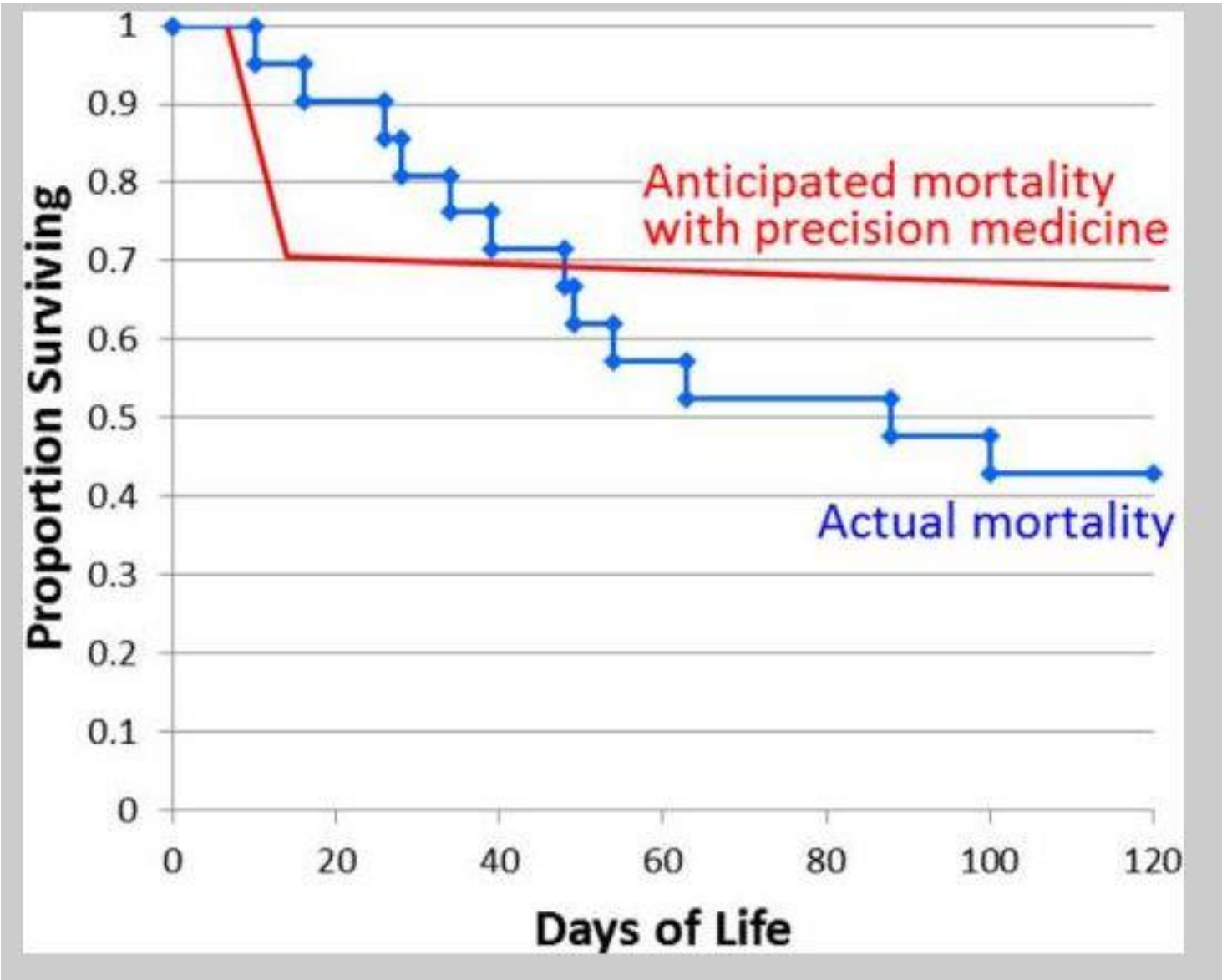
- Dr Kingsmore
- Initiate research protocols to obtain WGS
  (infants and parents)
- $$$

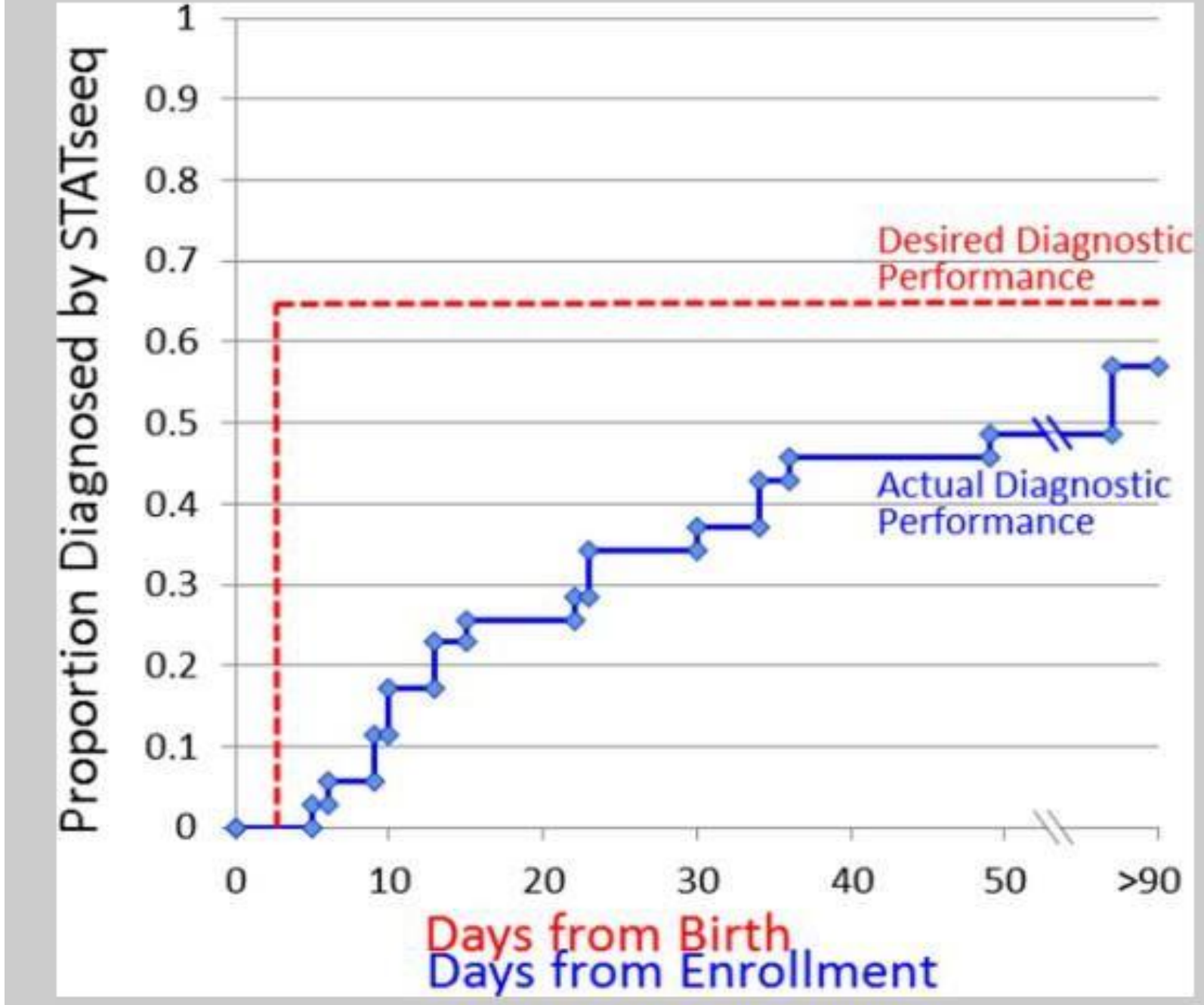
2015

- Precision medicine initiative
- WGS in 26 hrs

Precision Medical Management Following Rapid Genetic Disease Diagnosis in The NICU

1. Psychosocial benefits for parents (answers, knowledge of prognosis, planning, psychological and religious Support).
2. Precision treatments for affected infants that prevent death, diminish disease severity, delay progression or improve quality of life.
3. Earlier avoidance of futile or painful treatments, unnecessary of invasive testing, and planning of withdrawal of care.
4. Time to plan and implement investigative new treatments
5. Basis for increased coordination of care among providers
6. Genetic counseling regarding recurrence risk
7. Parental referral to specific Support groups
8. Reduced lifetime cost of care


Proportion Surviving
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
20
40
60
80
100
120
Days of Life
Anticipated mortality
with precision medicine
Actual mortality


Proportion Diagnosed by STATseeq
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
10
20
30
40
50
>90
Desired Diagnostic Performance
Actual Diagnostic Performance
Days from Birth
Days from Enrollment

Traditionally, genetic testing has been too slow or perceived to be impractical to initial management of the critically ill neonate. Technological advances have led to the ability to sequence and interpret the entire genome of a neonate in as little as 26 h. As the cost and speed of testing decreases, the utility of whole genome sequencing (WGS) of neonates for acute and latent genetic illness increases. Analyzing the entire genome allows for concomitant evaluation of the currently identified 5588 single gene diseases. When applied to a select population of ill infants in a level IV neonatal intensive care unit, WGS yielded a diagnosis of a causative genetic disease in 57% of patients. These diagnoses may lead to clinical management changes ranging from transition to palliative care for uniformly lethal conditions for alteration or initiation of medical or surgical therapy to improve outcomes in others. Thus, institution of 2-day WGS at time of acute presentation opens the possibility of early implementation of precision medicine. This implementation may create opportunities for early interventional, frequently novel or off-label therapies that may alter disease trajectory in infants with what would otherwise be fatal disease. Widespread deployment of rapid WGS and precision medicine will raise ethical issues pertaining to interpretation of variants of unknown significance, discovery of incidental findings related to adult onset conditions and carrier status, and implementation of medical therapies for which little is known in terms of risks and benefits. Despite these challenges, precision neonatology has significant potential both to decrease infant mortality related to genetic diseases with onset in newborns and to facilitate parental decision making regarding transition to palliative care.