

Information challenges in the Life Sciences: DNA-based diagnostics

William Baines

Merlin Ventures

<http://www.users.dircon.co.uk/~merlin2>

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The prospect of talking about gene chips, diagnostics and information both exhilarating and depressing.

Exhilarating because, as a confirmed techno-freak and one of the originators of what is now called Sequencing By Hybridization, I am always grateful for an opportunity to talk about DNA chips, one of the most elegant technologies to come out of the marriage of molecular biology with miniturization and semi-conductor technologies

Depressing for three reasons.

Firstly, because the BIA has once again spelt my name wrong - thank you, John

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Secondly, because I have to pack it all into ten minutes

Thirdly, because the applications of advanced DNA technologies to diagnostics is so limited, and the limitation has little to do with the technology, or its associated information problems.

I am going to offer an idiosyncratic view of why this is so, and some hints as to where it leads us.

An information challenge

- Finding data
- Turning it into knowledge
- Delivering the knowledge to the right people



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There is an information challenge here. Finding out the genetic data requires sophisticated information handling and processing.

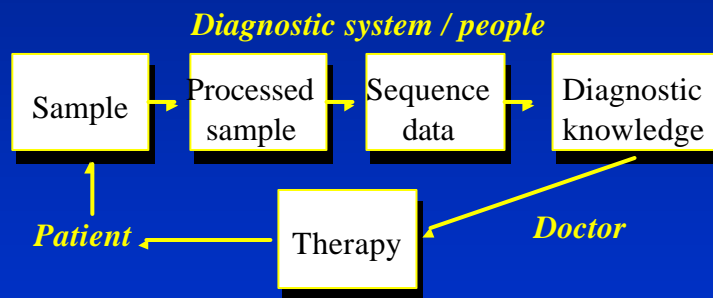
That information also has to be turned into knowledge, the ability to make decisions.

And that knowledge has to be delivered to people who can use it.

Advanced DNA analytical technologies are usually discussed in the context of discovery, but here, I submit, there is not much of an informatics challenge. There are huge technical tasks, but the people concerned, several of whom are speaking today, know how to solve those problems. Usually the solution involves the highly parallel application of that most reliable of IT technologies - lots of money.

Applying the same technologies to diagnostics however requires the solution of information problems of a different order. An intermediate problem is the use of DNA information in therapeutics development, which I shall touch on.

Elements of DNA diagnostics



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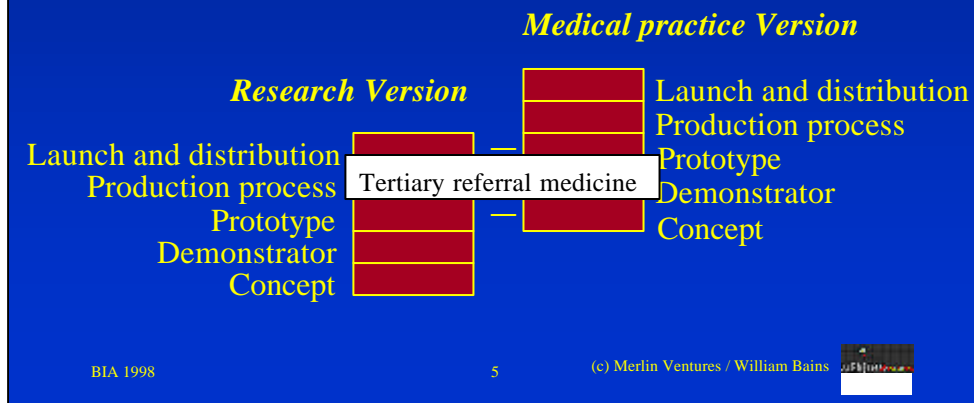
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Let us look at the steps involved in using a DNA analytical technique in diagnosis, and see how far the various technologies have got. The scheme here is fairly simplistic - we do not have time for a more detailed analysis today.

Development path for DNA diagnostic technology components

- Research driven technologies used in research first
- Sometimes never make it to medical practice



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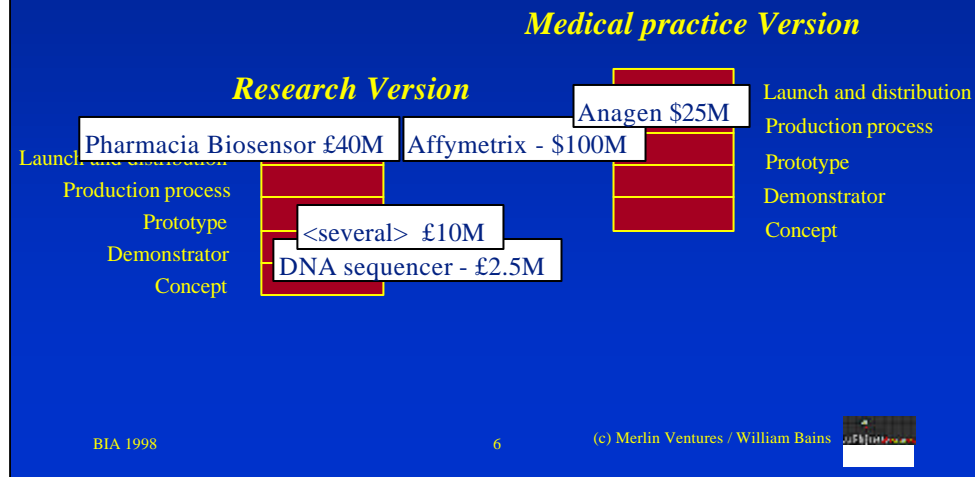
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DNA technologies are quite typical of high-tech developments with potential diagnostic applications in being developed in two stages - a stage where the technology is developed as a research tool,

and one where it is developed as a true diagnostic.

Use of the technology in tertiary medicine falls in between the two, as tertiary referral centres apply well-validated research tools to medical practice. In some diseases, such as rare genetic conditions, tertiary referral centres are the only centres. DNA technology has penetrated here quite fast, but these are tiny markets.

Development costs for DNA diagnostic technology components



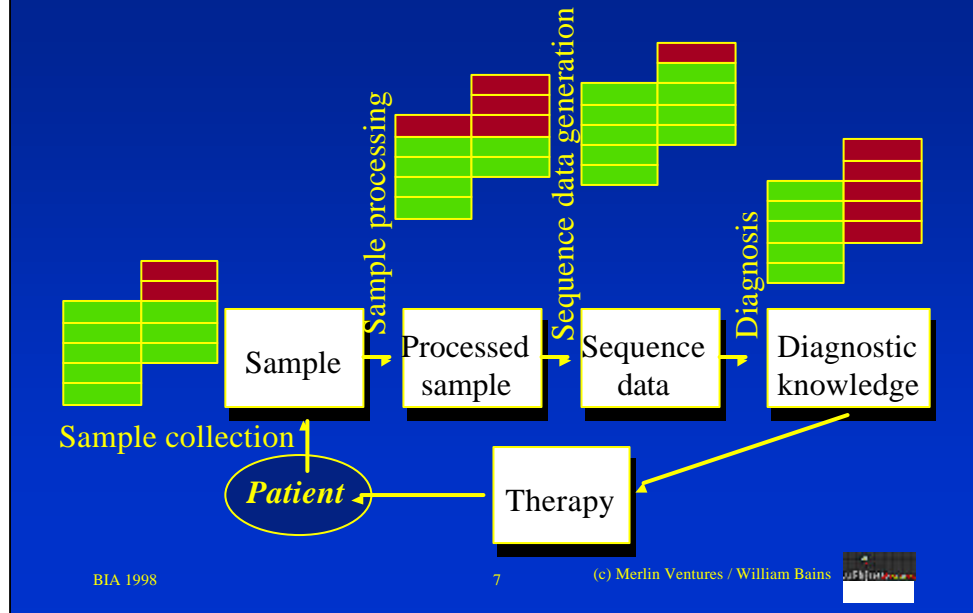
The costs of getting up the research side of this diagram are substantial. The additional costs of getting up the medical diagnostic side are also substantial.

(These are actual examples, some of which are confidential, however.)

So no-one is going to do this unless they have a clear idea of what they are going to sell at the end of the day.

This is why development of the medical diagnostic side of DNA technology has been so patchy ...

How far are we from routine DNA diagnostics?



For the mainstream of medicine, development of the technology is less advanced, but is getting there. One aspect that has not been developed far is the routine use of the data gene chips and similar technologies generate for diagnosis.

This is not because of a lack of technological development. From its inception in the late 1980s, gene chip technology development has been very fast:

Data vs Knowledge vs Information

The machines generate data

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0100100100111010101000100010011111010101001  
agtcgtcgagttaccacgcttgcacacatcgacaccattctacgct
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The researcher wants information



The clinician needs knowledge

Aspirin vs Imigram

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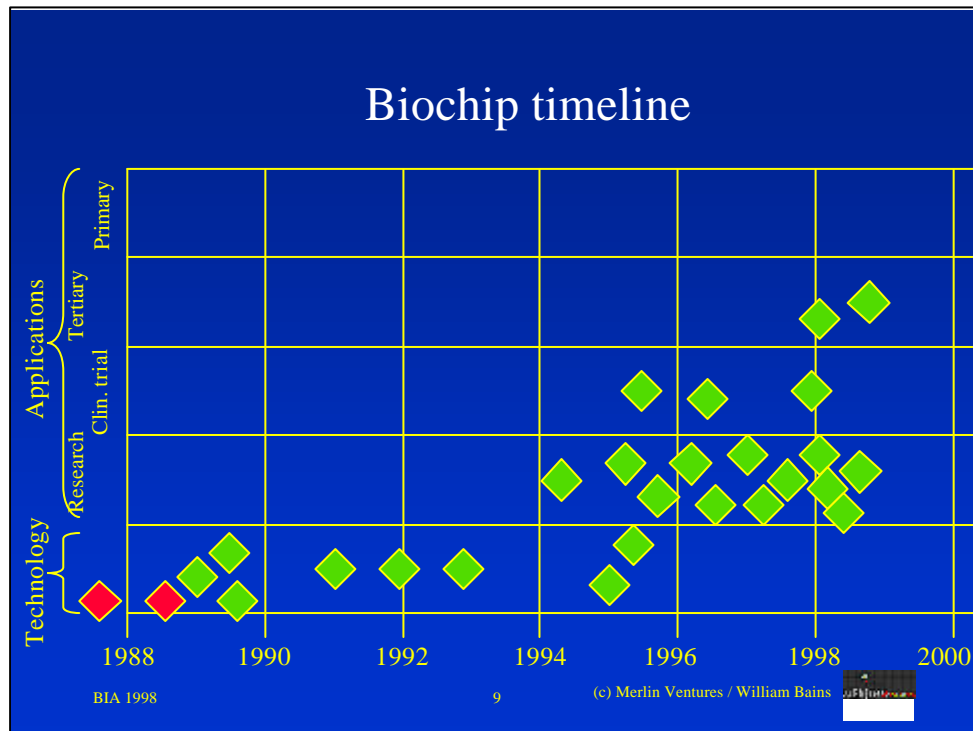
The biggest disparity is in informatics. I have distinguished between the research informatics, where the problems are ones of information handling, and medical informatics, where the problems are ones of knowledge generation.

While research informatics - turning the swarm of bytes from a sequencer into readable information - is a major technical challenge, it is one we knew how to solve in 1980: indeed, most of the basic algorithms for sequence matching and comparison date from that era. So the question is one of speed, efficiency, and not drowning the researcher.

Medical informatics is a different issue, because nearly all that data is irrelevant to medical practice as it is performed.

The doctor wants information in the knowledge structure of contemporary medicine, not that of molecular genetics. And it is very hard to convert DNA chip data to a model based on 1940s clinical chemistry.

It has worked sometimes, which I will mention. However nearly all the achievements in DNA chip technology, totalling at least \$350M investment, have been in research with a few excursions into tertiary medicine ...



This disparity between medicine and research has been reflected in the development of chip technology. From a handful of founding patents and papers there has been rapid, systematic development of the base technology

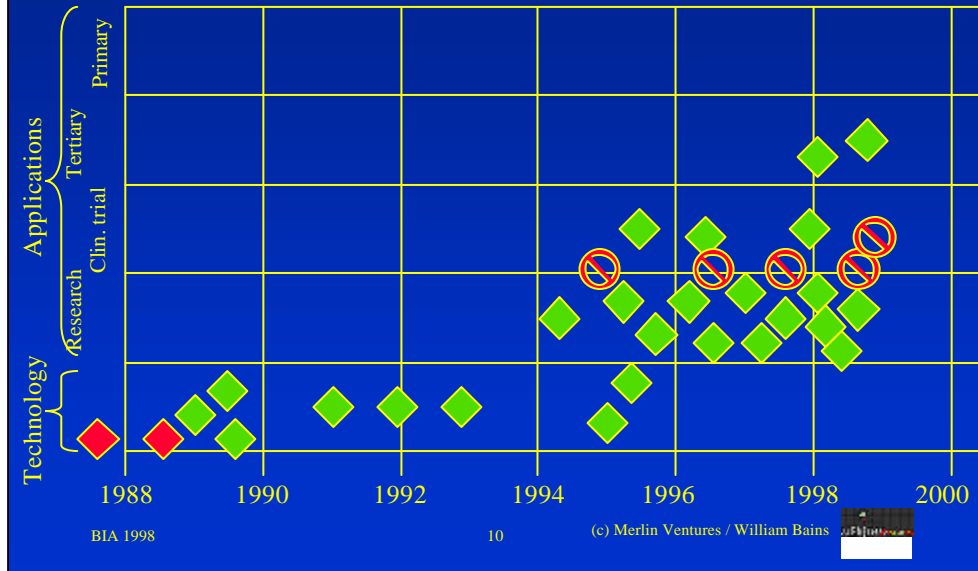
followed by its application to research (primarily genomics)

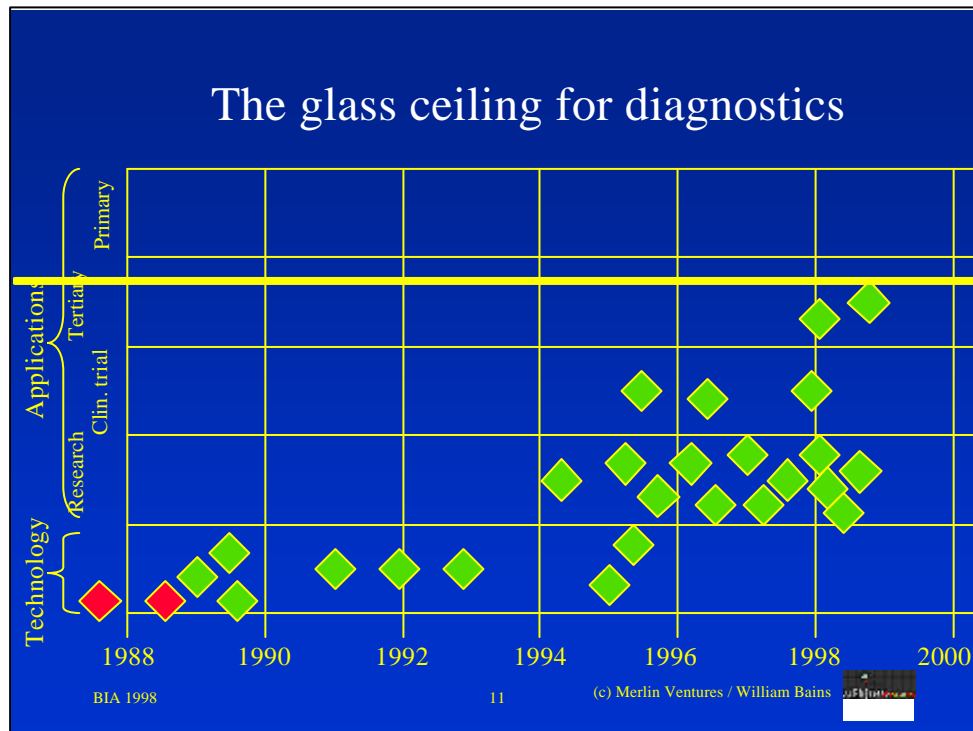
and recently its application to specialist medical therapy

(I include here milestones of actual achievement, not founding a company or publishing a press release)

And this being biotech, of course this is accompanied by frequent and acrimonious patent disputes ...

Biochip timeline



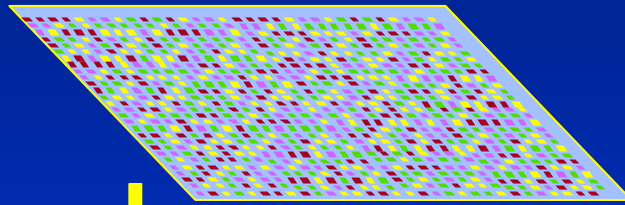


I do not believe that this trend is going to continue into an application in more general healthcare, despite the promises of market analysts and gene chip companies, because we need a different paradigm for its application.

There is in effect a glass ceiling, blocking its more general use

The glass ceiling is the medical profession itself.

Barriers to wider use of biochips



- **Highly multiplex analysis**

- ~~infectious disease~~
- ~~cancer genetics~~
- ~~virological genetics~~
- ~~predisposition analysis~~
- ~~therapeutics response~~
(pharmacogenomics)

Physicians do not diagnose this way

Drugs are not developed this way (yet)

Being applied to HIV - but how general is this?

No-one (no doctors) want to know

Valuable for trials, but not for prescribing?

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In principle, biochips could be applied to many disease states ...

but the reality is that in each of them, although the technology has been 'just 5 years away' for 20 years, there has been no driver from the medical community to apply it

Cancer is a particularly illustrative example. Although in the early 1990s oncologists all said what a good idea oncogene typing would be, the Oncormed and Myriad tests for BRCA-1 have been dismal commercial failures, with astonishingly low take-up rates even among predisposed families.

When has this not applied?

- AIDS / HIV therapy
- Rare diseases (especially Mendelian recessives)
- Doctors (make the worst patients ...)

- “Trust me, I’m a Doctor...”

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This argument has not applied in three areas, and all three have one feature in common - the patient, not the doctor, drives the therapeutic regime.

In all others, the doctor is in the driving seat, and they simply do not have the time or expertise to handle the megabytes of sequence and mapping data generated by a GeneChip or an ABI system, let alone the gigabytes of ancillary information necessary to link that data to general healthcare.

This will change if either of two things happen.

Yet another b***** revolution

- Highly multiplexed DNA diagnostics will come into their own when:
 - Drugs really are developed to target the molecular basis of disease
 - Patients seize control of the biomedical process

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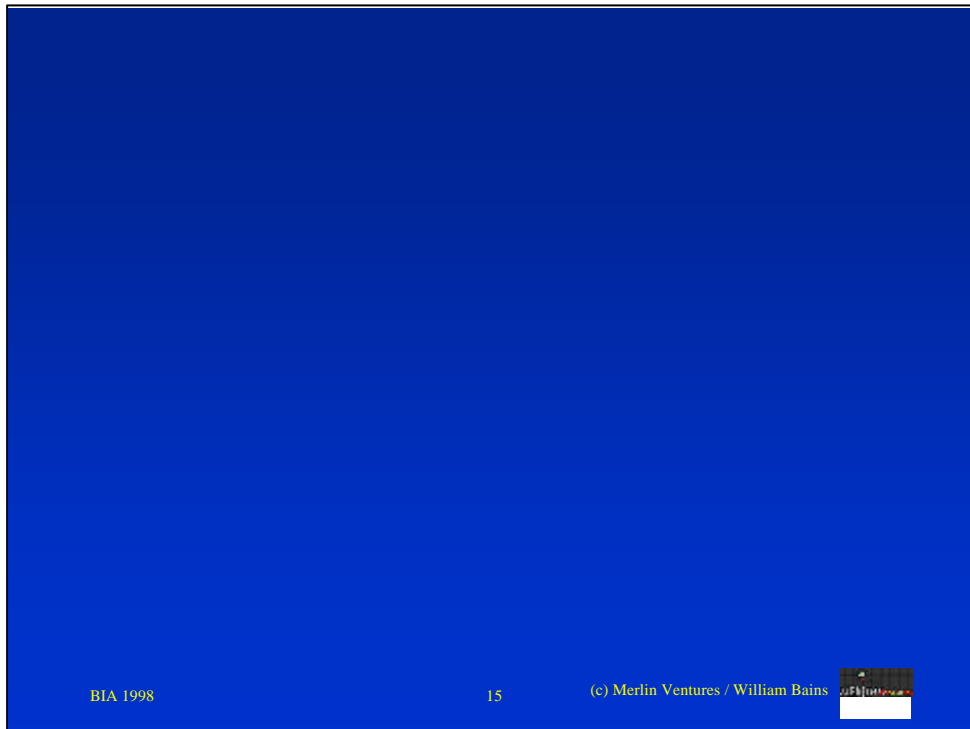
Viagra illustrates both these points.

Viagra may end up as the most commercially successful drug ever. But it was not discovered or put into development for male impotence. All the talk about rational drug design is still that - talk.

And for those who say 'now we really do rational, genomics targeted, combichem supported, structure-based drug design', I would cynically point out that they said the same thing every time a new 'revolution' happened in therapeutics discovery in the last 30 years, and they were , well, let's say 'misguided'

Illustrating the second trend, patients are starting to demand Viagra, and finding ways to obtain it, side-stepping the medical profession.

Ironically, diagnostics has preceded therapy in this trend by 20 years, with home pregnancy and cholesterol tests. But these have not come through conventional healthcare systems. They have arrived from technology being applied to customers (not tertiary referral specialist) in completely new ways. They have rendered conventional medicine irrelevant



If you think this is not a trend for the future, or that it is only something that applies to ageing Californian technocrats with stress-induced impotence and their own ISDN line, go into any urban secondary school in this country and ask the children there about CNS pharmacology. The results will probably astonish you.

They scare the hell out of me.

Diagnosis, illness, and the nature of life

- DNA diagnostics will expand into specialist, high-tech tertiary medicine.
 - information handling issues, solvable with big computers
- Genetics-based stratification will expand into clinical trials
 - will drive much better sample processing, and radically drive down per-test price
- All sorts of diagnostics will expand into patient-driven life-care
 - require radically new information paradigms
 - will be derived from DNA-based research, but will not necessarily be DNA-based tests
 - the doctors will not like it - but who cares?

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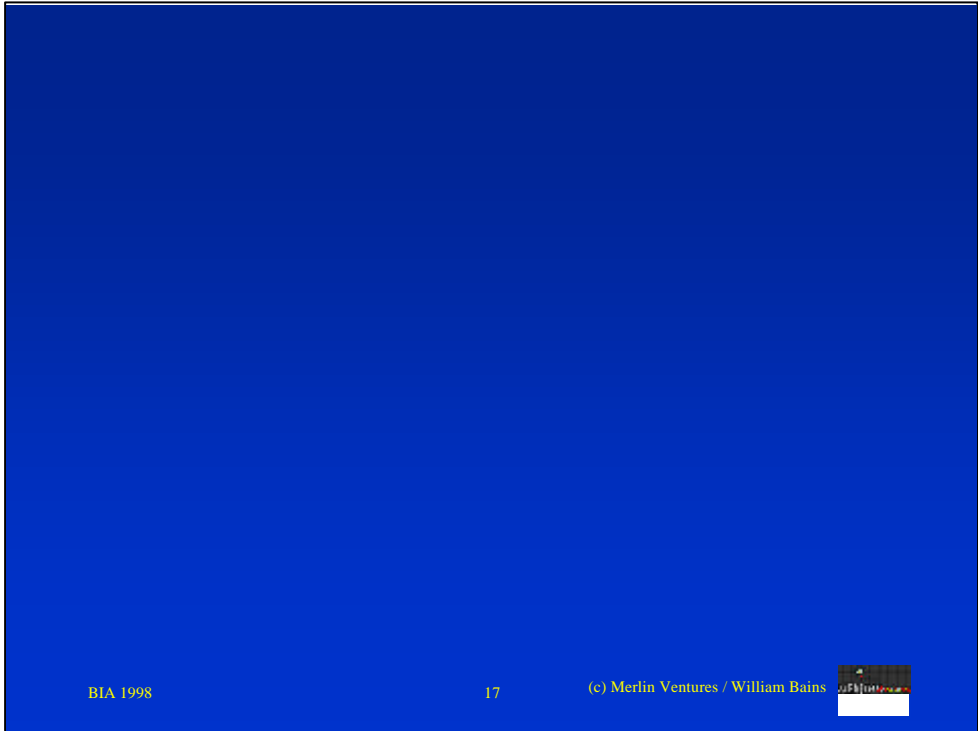
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So, to end on something you can all disagree with, here are some forecasts for the future DNA-based diagnostics will expand into complex, expensive, tertiary care medicine. There is no fundamental information issue here that cannot be solved with big computers, which in ten year's time will probably mean something you can loose among your small change.

Use of genostratification in clinical trials will expand hugely, and because of the purchasing power of CROs and major pharma, the cost will decline precipitously.

The real use of the data will be in new modes of health-care. whether that is delivered through gene chips or through other technologies will depend on how flexible they are to the emerging needs not of specialist medics but of the health-seeking public.



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