

Formal genetic analyses

- tests genetic influence in etiology of disease
- identifies modes of inheritance of genes
- identifies gene loci on human genome

Segregation Analysis – using KC indices – 1500 KC patients from 200 families

- REJECTED

No major gene <.001

Sporadic <.005

Environment <.005

Additive <.010

- NOT REJECTED

Major gene >.10

Recessive > .90

Dominant > .90

Segregation Analysis

(related topographic measures)

Conclusions

- Keratoconus - genes implicated in disease
- Segregation ratio of 0.25 - multigenic inheritance i.e. inheritance cannot be explained by simple mendelian inheritance - 2 events required to cause keratoconus
- Consistent with heterogenous disease - i.e. both dominant and recessive
- Environment as the sole cause excluded

Is Keratoconus Genetic?

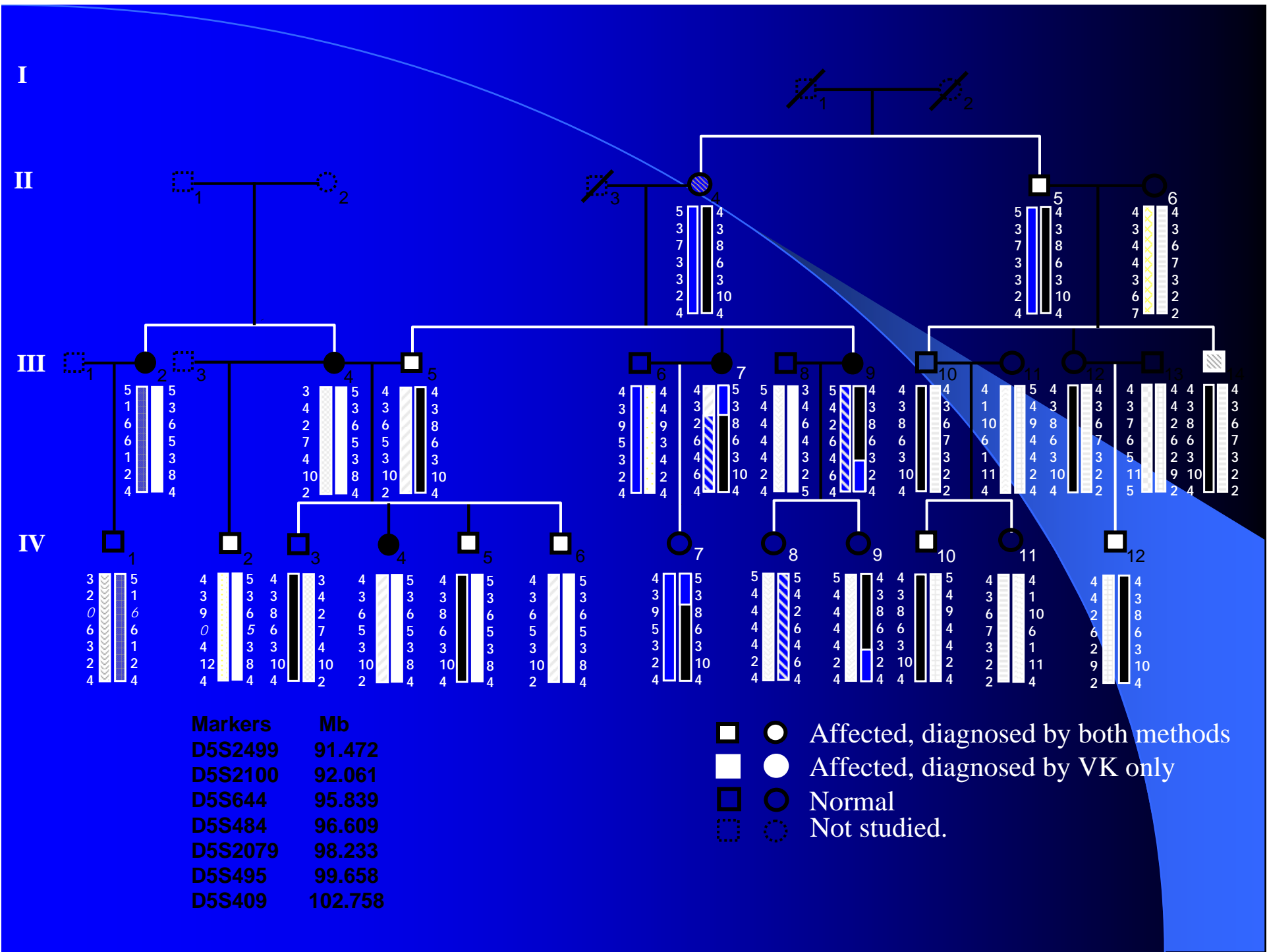
- Clearly these studies demonstrate that genes play a major role in the pathogenesis of the disease
- Other causes such as environmental factors(eg eye rubbing) may contribute to the expression of the disease, but by themselves are not the sole cause of keratoconus

How do we identify genes causing keratoconus?

- Identify suitable families for study
- Adequately phenotype them, using corneal topography (pattern analysis and quantitative indices (KISA% index already described))
- Collect and store their DNA
- *Gene linkage analysis* -identifies gene loci

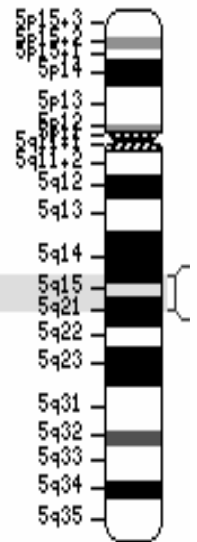
Gene Loci – Linkage analysis

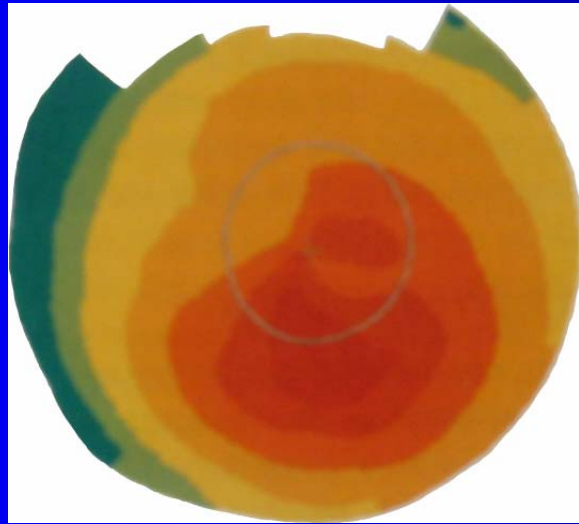
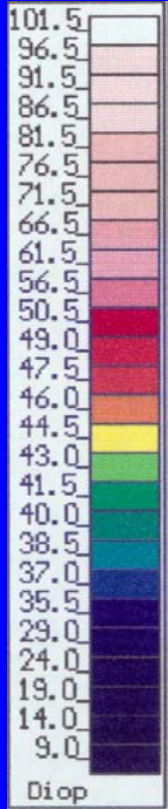
- **16q - Tyynismaa H** *Invest Ophthalmol Vis Sci* 2002;43:3160-3164
- **20q12- Fullerton J.** *Australia Hum Genet* 2002;110:462-470.
- **3p14-q13- Brancati F.** *Journal of Med Genet* 2004;41:188-192
- **20p* Heon E.** *Hum Mol Genet* 2002;11:1029-1036.
- **2p24.1- Hutchings H, Malecaze F** *J Med Genet.* 2005
Jan;42(1):88-94.



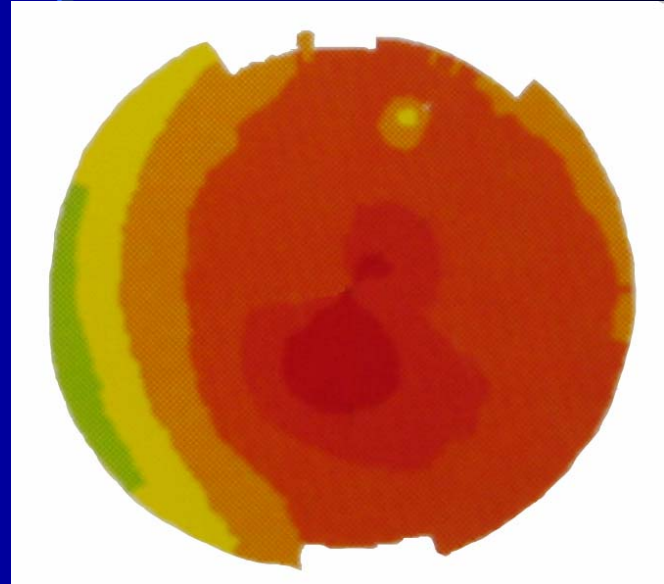
New Gene Locus 5q14.3- q21.1

- 6 cm region (LOD 3.53)
- *(Genetics in Medicine(In Press))*
- A two-stage genome-wide screen of a single autosomal dominant family
- **Topography key to accurate linkage analysis**





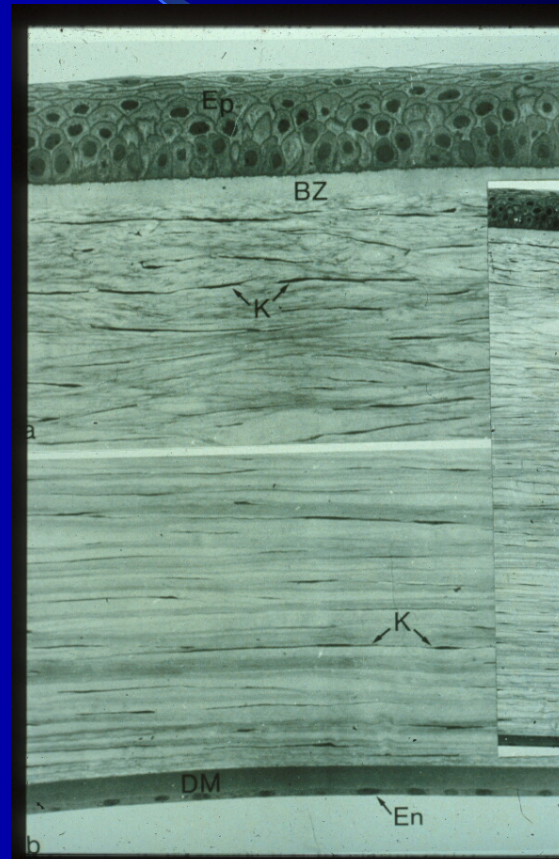
II-4



III-14

A new genetic approach- GENE EXPRESSION

- Can identify genes expressed in the cornea
- Compare diseased corneas with normal corneas and identify genes that are absent or suppressed
- May allow for gene therapy by increasing expression of suppressed gene

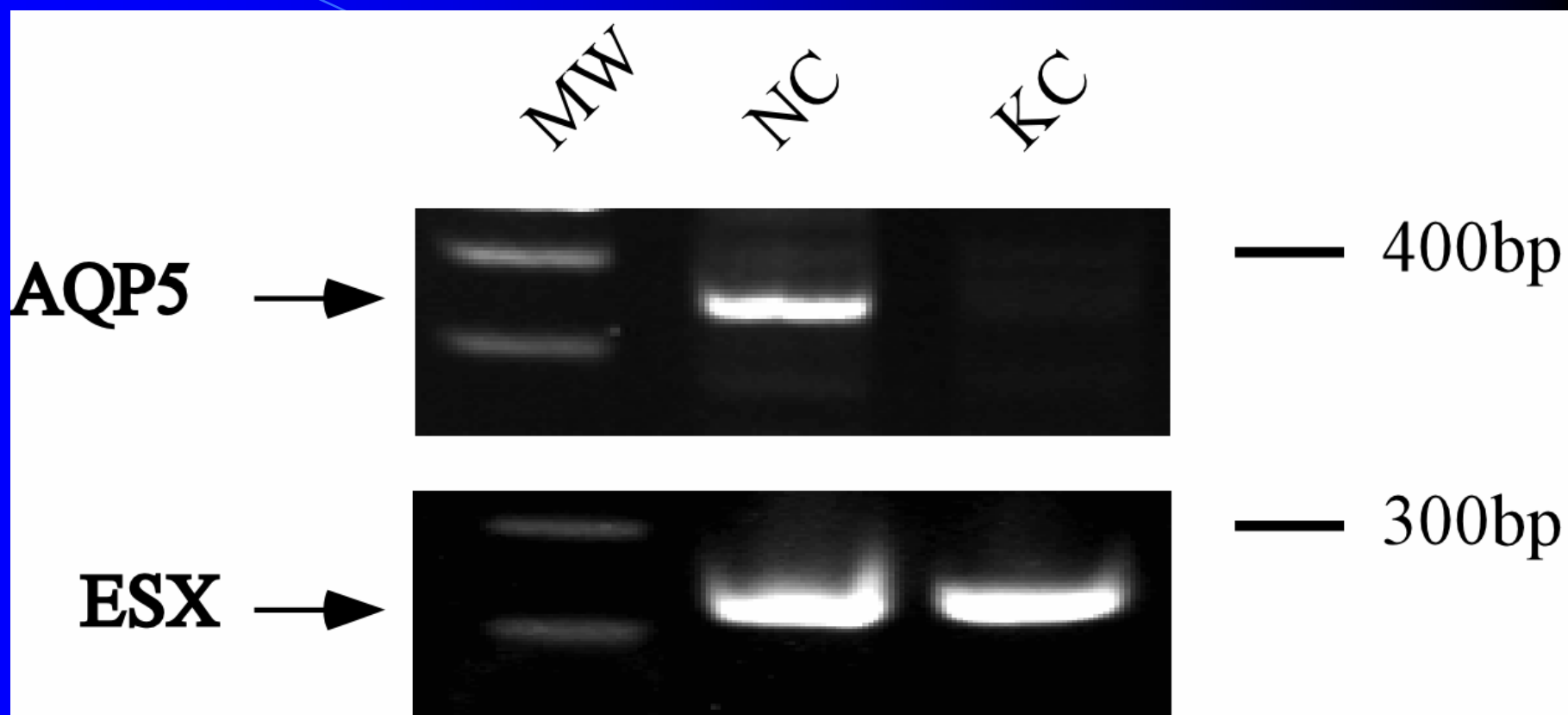


Methods: cDNA Library construction

1. 7 KC buttons immersed in *RNA/later* at time of transplant
2. Corneal buttons were pooled total RNA extracted
3. After analysis able to identify 4109 corneal genes
4. The largest library of corneal genes ever identified
5. Available to be viewed in its entirety at [www. Neibank.gov](http://www.Neibank.gov)

Invest Ophthalmol Vis Sci 2005 April 46(4) 1239-46.

AQP5 – absent in Keratoconus



INTACS FOR
KERATOCONUS
using the
Femtosecond
(*INTRALASE*) Laser

History – INTACS for Keratoconus – pioneered by Dr. Josep Colin

- **2001 published results on 10 eyes**
- Technique: 0.45mm inferiorly, 0.25mm superiorly – temporal incision-10 0 nylon suture removed at 1-4 weeks
- Patient characteristics: contact lens intolerant, clear central cornea, BCVA 20/100 or better, corneal thickness at least 400um incision;central pach 479(32)um

Colin 2001 - results

- UCVA mean – pre 20/200 - post 20/50
- BCVA mean - pre 20/50 - post 20/32
- Astig mean - pre 4(2 sd) - post 1.3(1.4sd)
- K readings - pre 53.2(3.0) – post 48.6(2.8)
- Topography - reduction in cone size
reduction in SAI and PVA
no change in SRI or sim K

No correlation betw preop myopia and UCVA

Decreased BCVA with increased residual myopia

Intralase acquired June 2003

Goal of study

commenced January 2004

- To determine the efficacy of inserting INTACS in the cornea using the Intralase to make the channels
- To determine the ideal parameter settings for optimal efficacy
- To compare the outcomes of INTACS inserted with the Intralase to its insertion with the mechanical spreader

Goal of Intacs for Keratoconus

Primary goal: to make a patient who is contact lens intolerant contact lens tolerant and thus prevent the need for a cornea transplant

Secondary goals: may allow for transition from rigid to soft toric lenses, may allow for improved acuity with spectacles only

Realistic expectations:

will still be dependant on visual aids

no evidence it retards progression

may not have any benefit, may make vision worse

Surgical Technique

- Preop refraction, pachymetry, topography
- Mark the center of pupil
- Center the Intralase cut around the center
- Entry site determined by topography
- Goal to insert INTACS to bisect thinnest area of cornea
- Avoid superior incision- neovascularization
- Thickness of INTACS chosen based on spherical equivalent and desired effect
- All entry wounds sutured with 10'0 Nylon

Intralase parameters

Entry cut: depth 400u,
length 1.4mm,
width 1mm

Channels size varied over time

6.6X8.6(1mm)

6.6 X7.6(0.5mm)

6.6 x 7.2(0.3mm)

INTACS - Oval cone – asymmetric 0.3/0.35mm

Nipple cone – symmetric .35mm

Mild cone – single INTAC

Intralase results

20 eyes with 6 month follow up

Change	Mean	Range
Average K	2.02	0.5 to 4.6D
Sph equiv	3.56D	1.5 to 7.0D
UCVA	3.42 lines	1 to 7.0 lines
BCVA	3.35 lines	0 to 7 lines
SRI	0.34	0.11 to 0.98
SAI	0.75	0.4 to 2.52

Intralase Nomogram

the tighter you make the channels the more effect you get

6.6X8.8 mm

UCVA	2
BCVA	0
Sphere	0.70
Cylinder	0.75

* Can get even more effect by making channels narrower than INTACS

6.6X7.4 mm

4
6
3
1.9

* One patient got as much as 8D of effect using 7.3mm

Ring size vs effect

Settings (mm)	Channel width(mm)	Decrease in average K	Number of eyes
8.6x6.6	1mm	0.73D	3
7.6x6.6	0.5mm	0.83D	3
7.4x6.6	0.4mm	2.94D	12

Intralase nomogram

The tighter you make channels the more effect you get

- Manufacturer initially recommended 6.6x8.8mm
- I recommend at starting off at 6.6x7.6mm and then reducing it to 6.6x7.2 or 6.8x7.4
- Leaves you with channel of 0.3mm which is 0.1mm narrower than the INTACS = .35mm

Intralase vs Mechanical

Change	Intralase (N=20) 3 mnths	Mechanical (N=10) 1 year
Average K	*2.02D	1.80D
Sph equiv	*3.56D	3.0D
UCVA	*3.42 lines	3 lines
BCVA	*3.35 lines	2.4 lines
SRI	0.34	*0.68
* Better result		

Intralase vs Mechanical#

#(Rabinowitz, Colin, Siganos)

	Intralase	Mechanical #combined avg
Average K	2.12	2.7
Sph equiv	*3.56	2.4
UCVA	*3.42	2.8
BCVA	*3.35	2.03

Contact lens/glasses tolerance

- **INTRALASE(3-6mths)**
- 6 months - 6/6(100%)
(BCVA 20/20-20/40)
- 3 months - 7/13(53%)
contact lens tolerant;
5/13(38%) final fitting not
attempted;
1/13(7%) experiencing
difficulty
- No explants required
- **MECHANICAL(1 yr)**
- 7/10(70%)
- 2/9 transplanted because
of fluctuating vision
- 1 explanted put in too
shallow

Advantages of the Intralase vs Mechanical

- Results of the two techniques are similar
- Intralase technique is simpler, quicker and guarantee depth of placement
- Can recut channel at a reliable depth if necessary
- Patient more likely to like the laser vs the blade
- High patient satisfaction rate: at 6 months 100% of patients happy with vision achieved with glasses or contacts and are contact lens tolerant

Problems/complications

- Unpredictable
- Because cut vertical, INTACS insertion might initially be technically difficult initially
- INTACS may move into wound site causing permanent wound gape
- Corneal edema if patient rubs eye and INTACS migrate to wound site
- Keratoconus might still progress despite INTACS

Case example 1

- 40 year old male – BCVA with glasses 20/70(plano –3.00D) wanted to improve his vision with glasses
- Single Intacs placed in steepest part of cone
- 1 Day postop = 20/20 with glasses with a prescription of +1.50-1.00X160



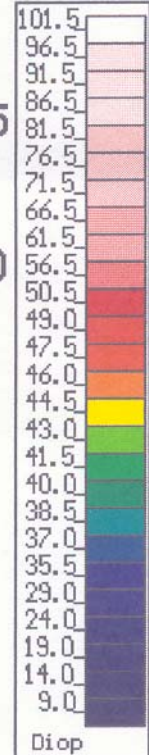
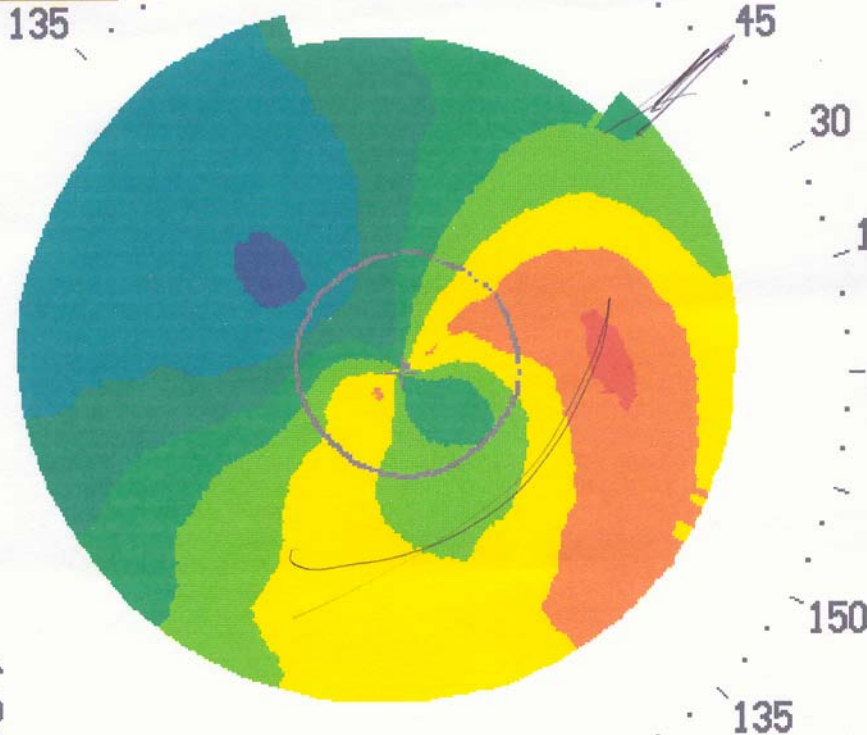
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SS#:

105 90 75 60
120

CORNEAL STATISTICS

SRI:1.03 SAI:0.90
PVA: 20/ 30 - 20/ 40
Sim K: 44.8 x 45 / 40.4 x 135
Min K: 40.2 x 142



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Y= 0.087

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03/12/2007

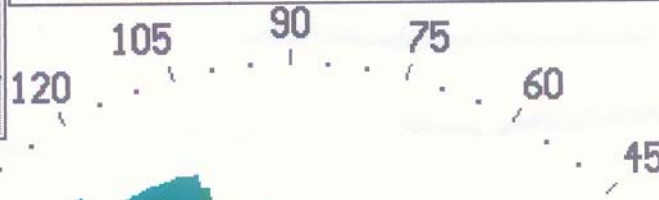
VA S 20/200
C 20/60

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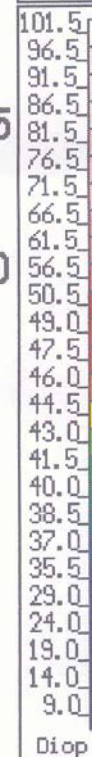
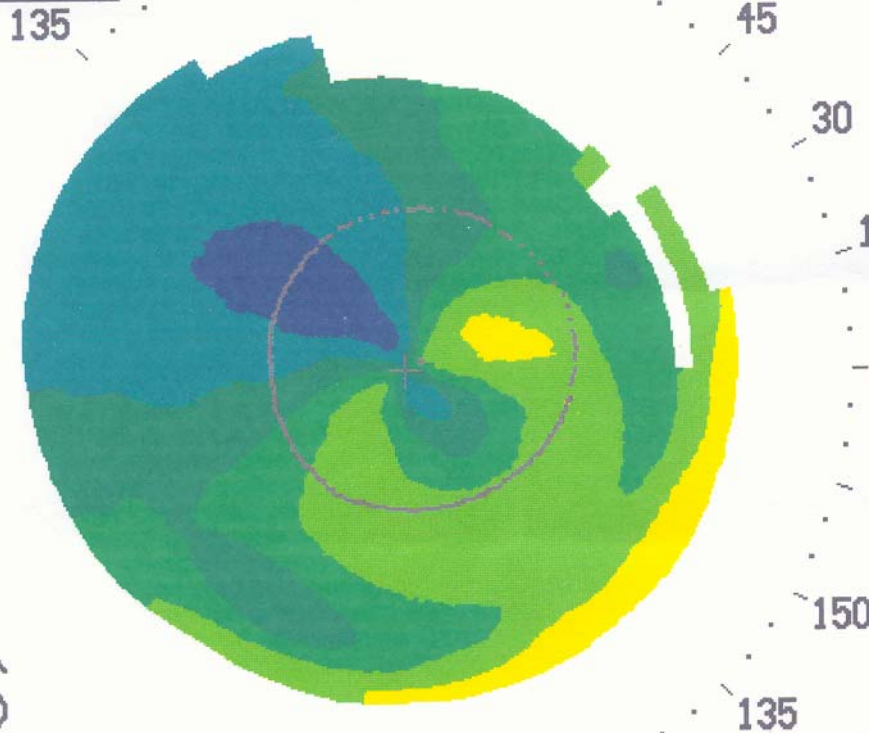
PATIENT: Valencia, Joseph
CLINIC#:

NONE
SS#:



CORNEAL STATISTICS

SRI: 0.95 SAI: 1.07
PVA: 20 / 25 - 20 / 30
Sim K: 42.9 x 37 / 39.1 x 127
Min K: 39.0 x 135



Press F1 Key
for HELP

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Ver:
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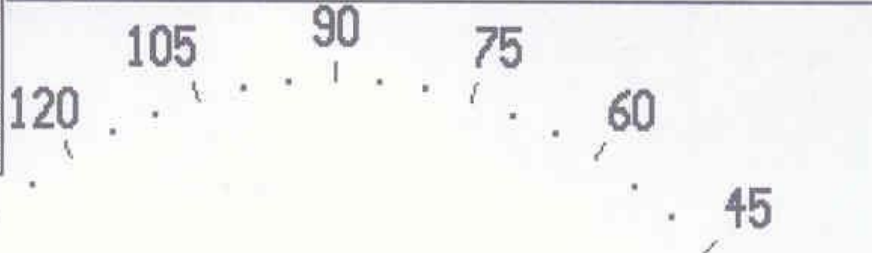
Case example 2

- 32 year old female contact lens intolerant
- VA = 20/70 with +1.50 -3.75 x 65
- Temporal incision placed – asymmetric
INTACS placed .3mm above, .35mm below
- Day 1 – 20/20 with a +3.50 Acuvue 2
disposable soft contact lens

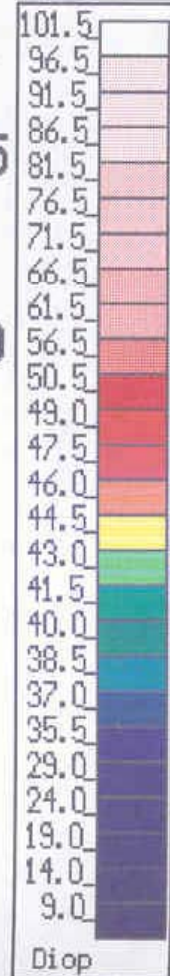
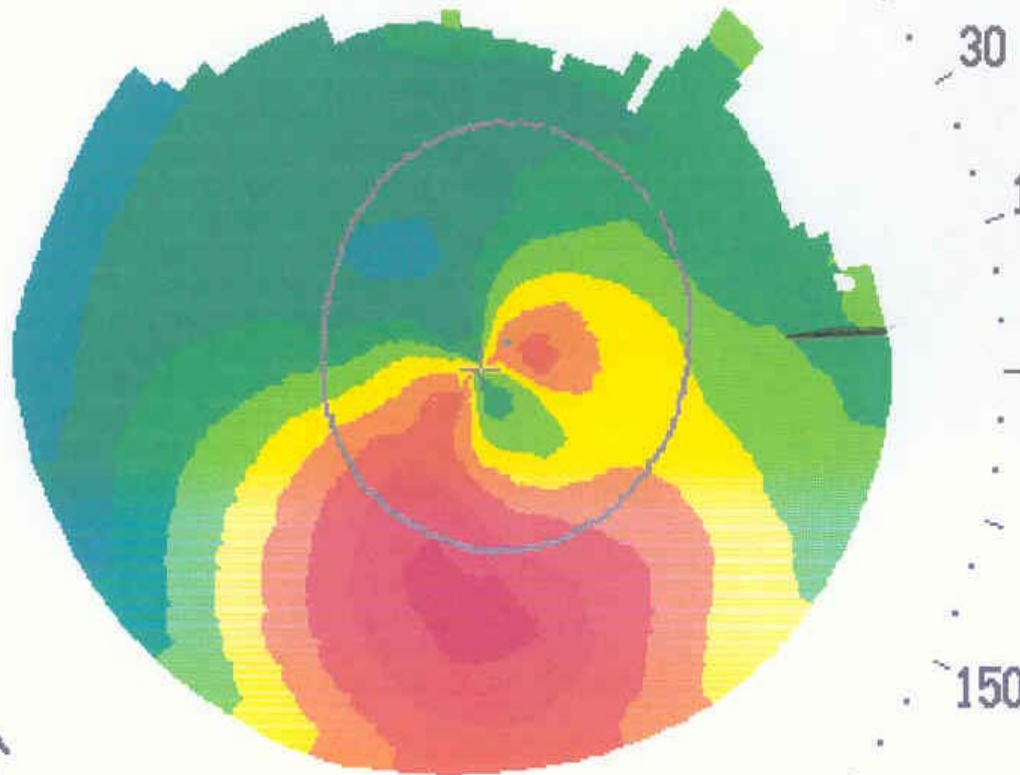


PATIENT: Christie, Debbie
 CLINIC#:

NONE
 SS#:



CORNEAL STATISTICS
 SRI: 0.82 SAI: 1.39
 PVA: 20 / 25 - 20 / 30
 Sim K: 45.9 x 38 / 41.6 x 128
 Min K: 41.5 x 135



Press F1 Key
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ABSOLUTE Ver: 1.61

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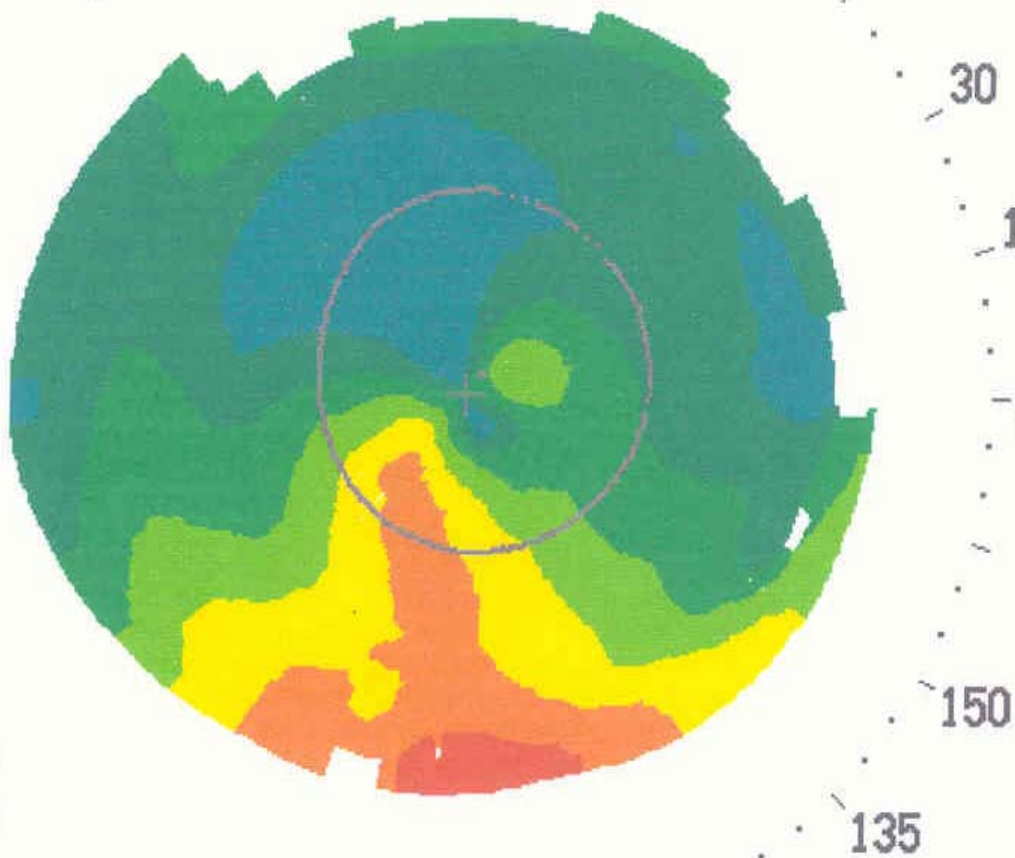


PATIENT: Christie, Debbie
 CLINIC#:

NONE
 SS#:

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 135 45

CORNEAL STATISTICS
 SPI: 1.02 SAI: 1.25
 PVA: 20 / 30 - 20 / 40
 Sim K: 43.2 x 45 / 40.3 x 135
 Min K: 40.2 x 142



101.5
 96.5
 91.5
 86.5
 81.5
 76.5
 71.5
 66.5
 61.5
 56.5
 50.5
 49.0
 47.5
 46.0
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 43.0
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 40.0
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Press F1 Key
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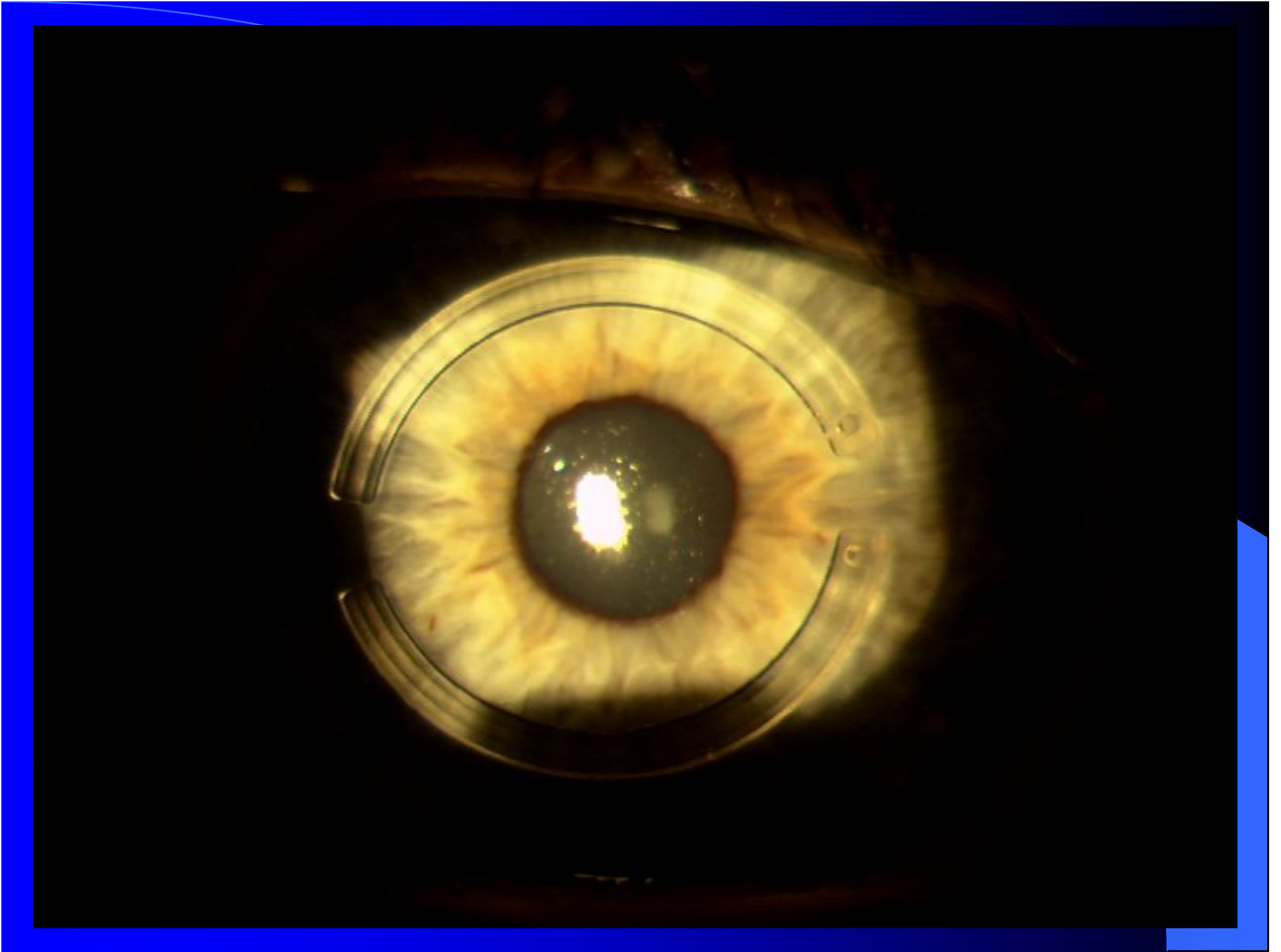
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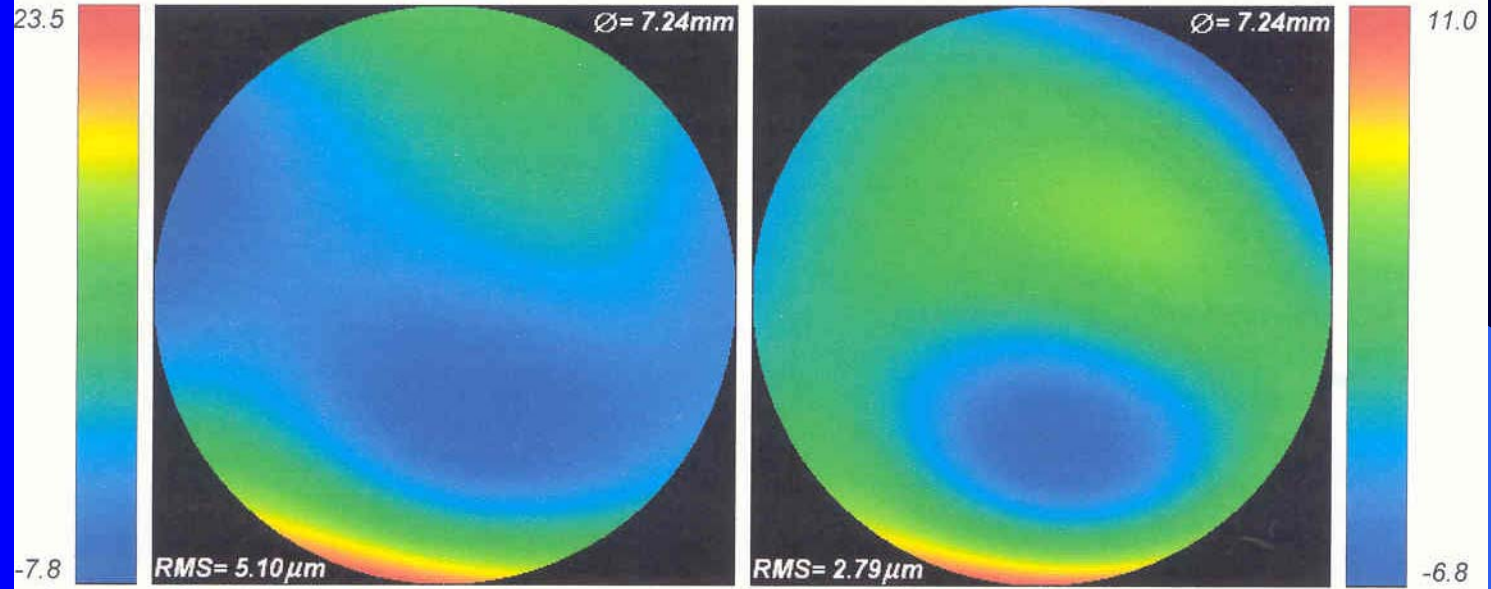
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 75 90 105

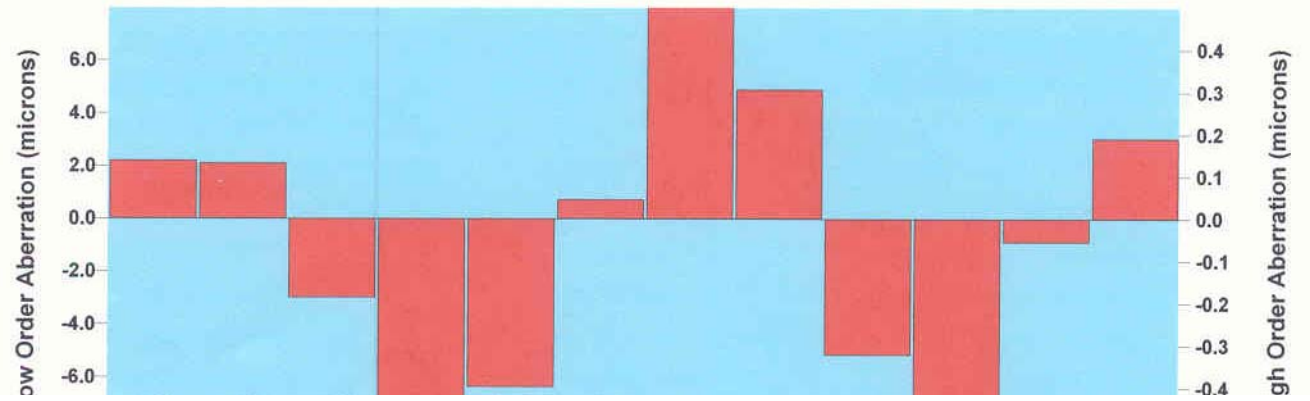


Refraction from Wavefront		Aberrations		RMS(microns)
Sphere	0.56 Diopters	Defocus		2.20
Cylinder	-2.28 Diopters	Astigmatism		3.65
Axis	130 Degrees	Coma		2.49
Match	45%	Spherical Aberration		0.31
Diameter	7.24mm	Other		1.24



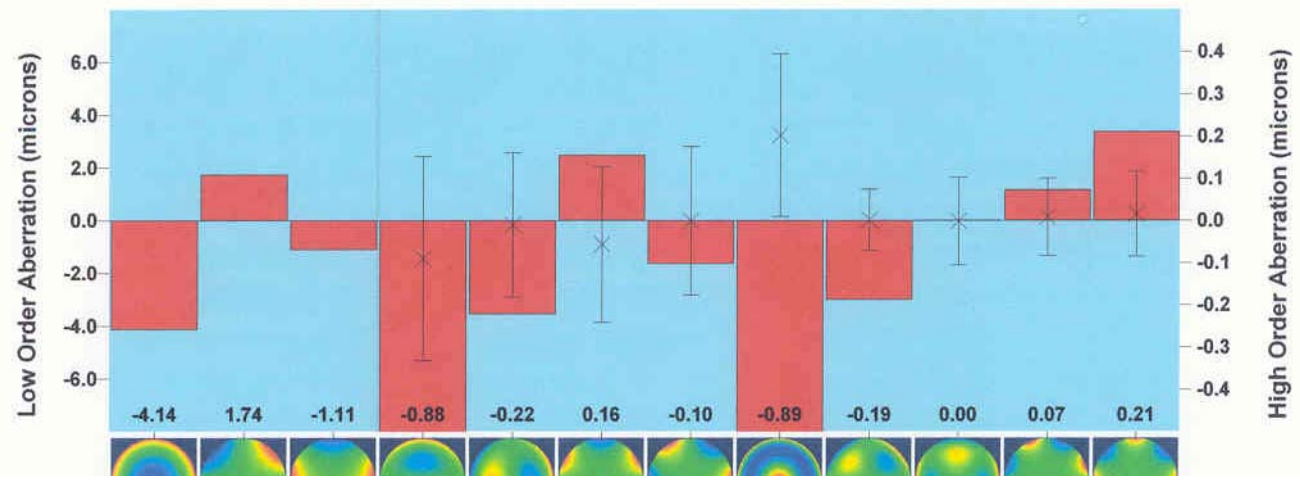
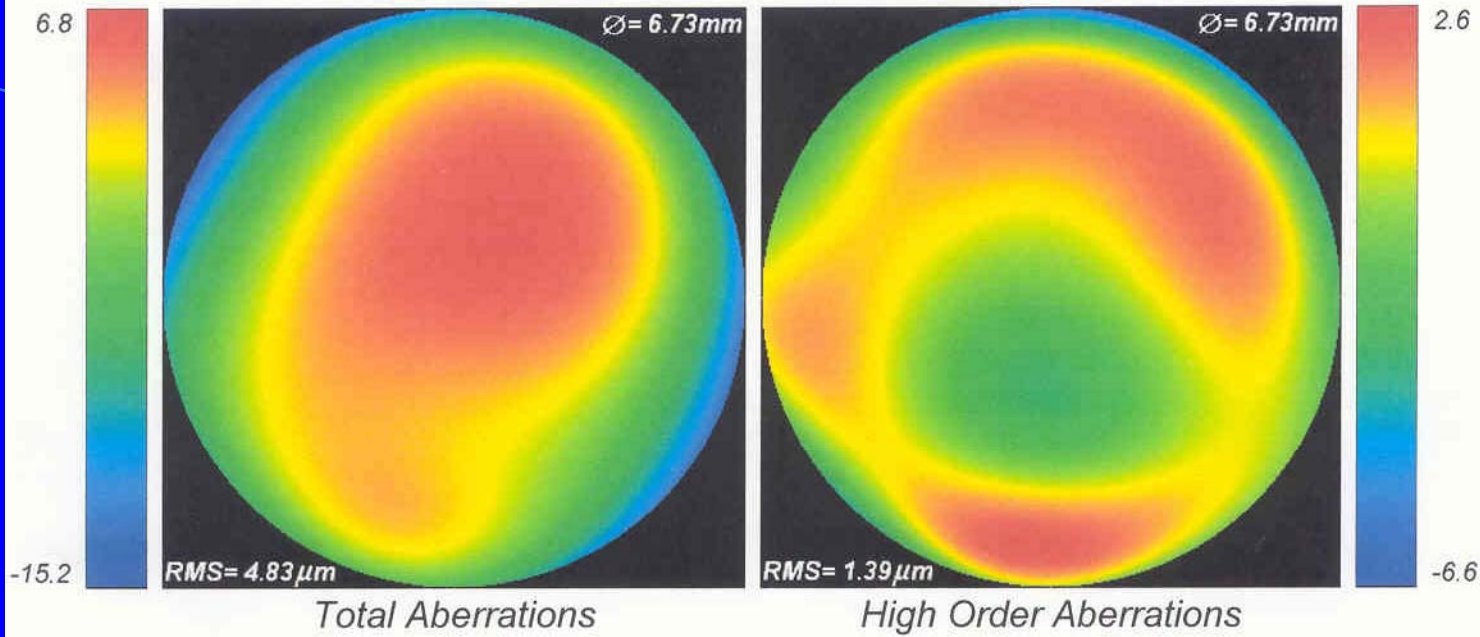
Total Aberrations

High Order Aberrations



<i>Sphere</i>	2.27 Diopters
<i>Cylinder</i>	-1.61 Diopters
<i>Axis</i>	136 Degrees
<i>Match</i>	71%
<i>Diameter</i>	6.73mm

<i>Defocus</i>	4.14
<i>Astigmatism</i>	2.07
<i>Coma</i>	0.91
<i>Spherical Aberration</i>	0.89
<i>Other</i>	0.56



Improvement in Wavefront data

	Pre-op	Post-op	% change
Astig	3.65	2.07	< 43%
Spherical	0.31	0.89	>187%
Coma	2.49	0.91	< 63%
Total RMS	2.79	1.29	<53%

Conclusions

- Results with Intralase similar those reported by Dr. Colin with the mechanical spreader, but is technically simpler once mastered
- INTACS- promising alternative to Corneal Transplants in select patients with keratoconus
- Patients with mild to moderate keratoconus do best, exclude patients with central scarring and central K readings in excess of 57D
- Dr. Colin is to be congratulated for his pioneering work which has significantly improved the lives of many patients with keratoconus

Medical Treatment for

Keratoconus?

Keratoconus – associated with inflammation/apoptosis

- Eye rubbing, contact lenses – causes chronic inflammation and apoptosis
- Evidence for apoptosis – tunnel assay studies^(Meisler, Rabinowitz, Wilson et al), increased apoptosis genes-expression studies^(Rabinowitz, Dong, Wistow)
- Aquaporin 5 absent – wound healing gene
- Increased dry eye in Keratoconus^(Tsubota)
- Inflammatory molecules demonstrated in tears of patients with keratoconus^(ophthalmology)

Potential medical treatment to stop progression(Restasis)

- Contains cyclosporine(0.02%)
- Inhibits apoptosis
- Decreases inflammation
- Treats dry eye
- May make eye more comfortable making eyes more contact lens tolerant, inhibit eye rubbing and inhibit chronic inflammation that may contribute to thinning of cornea
- Probably need stronger concentration of cyclosporine for maximal effect
- For the moment restasis is good/can do no harm

Merci Beaucoup



