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Supplementary appendix

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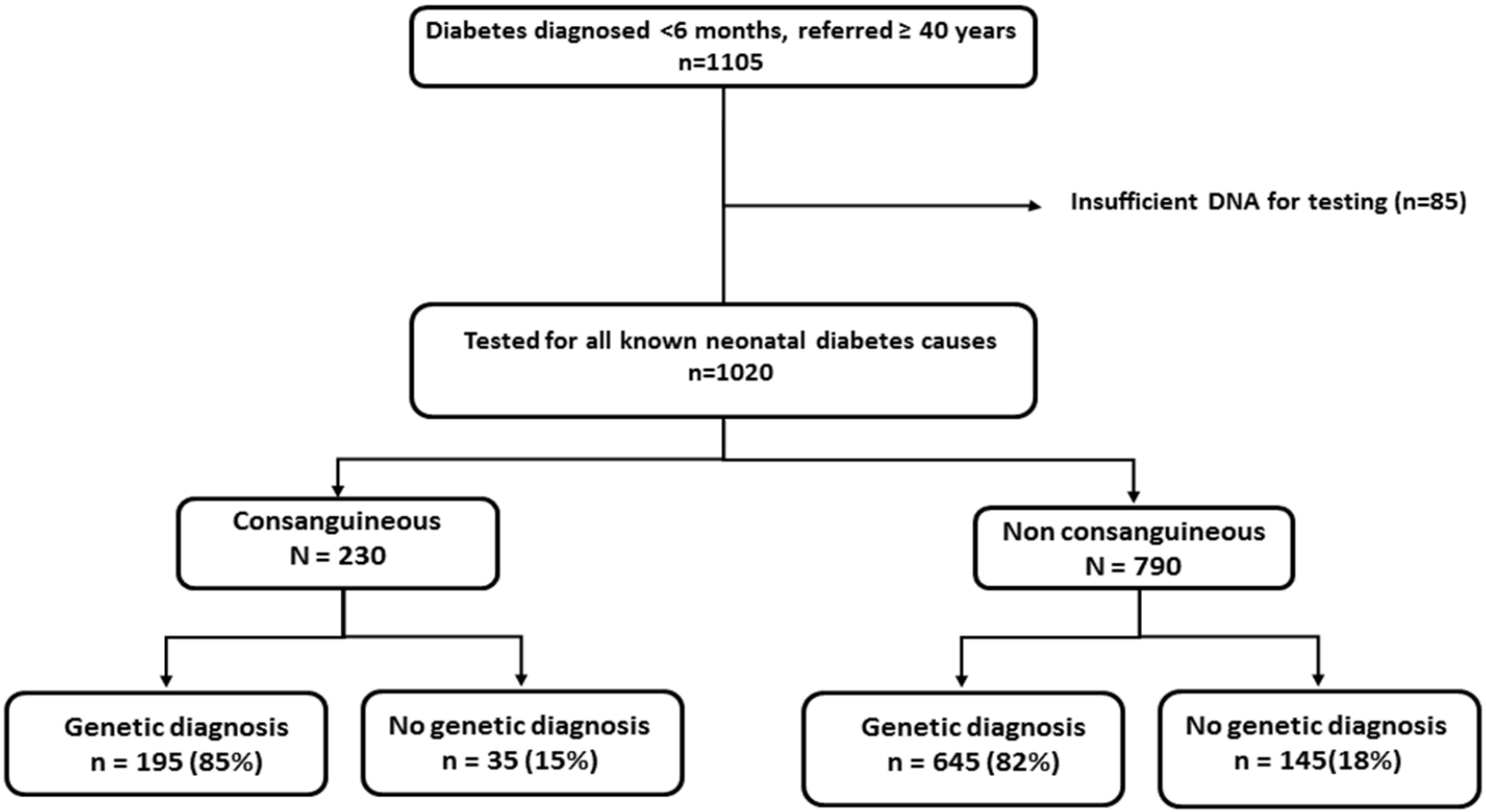
Supplementary Note

Genomic testing leads clinical care in neonatal diabetes: a new paradigm

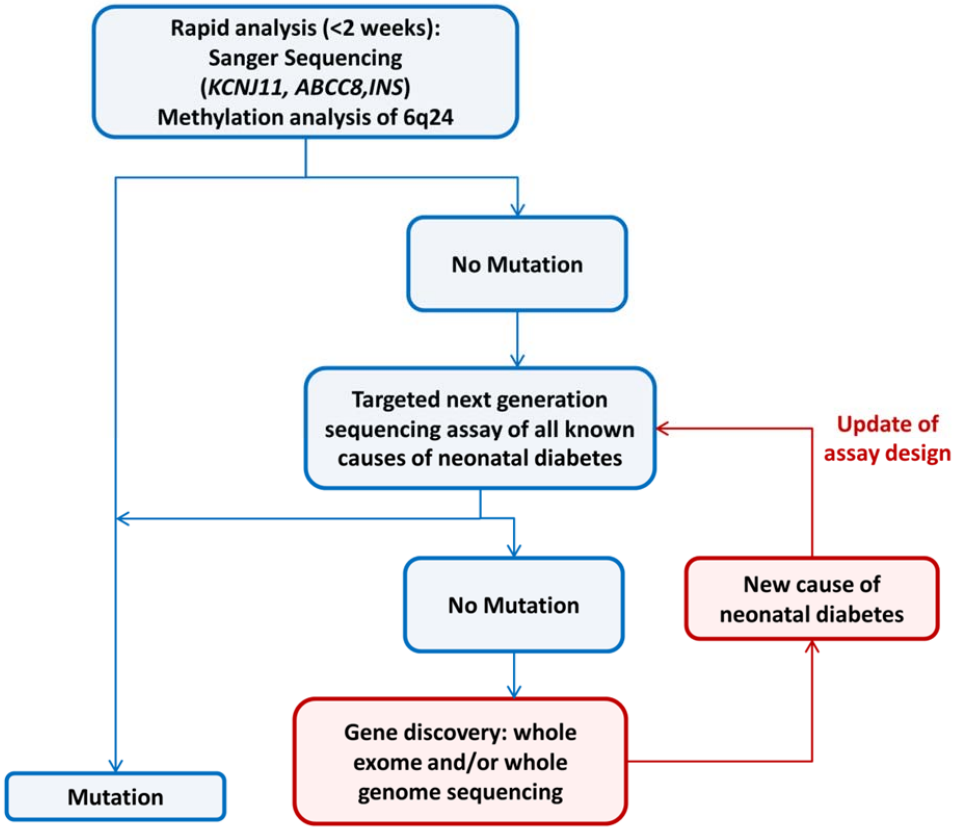
De Franco E[1], Flanagan SE[1], Houghton JAL[1], Lango Allen H[1], Mackay DJG[2,3], Temple IK[3,4], Ellard S[1] and Hattersley AT[1]

[1] Institute of Biomedical and Clinical Science, University of Exeter Medical School, EX2 5DW, UK
[2] Wessex Regional Genetics Laboratory, Salisbury Health Care Trust, Salisbury, UK
[3] Human Genetics and Genomic Medicine, Faculty of Medicine, University of Southampton, Southampton, UK
[4] Wessex Regional Genetics, Salisbury Foundation Trust and University Hospital Southampton NHS Trust, Salisbury, UK

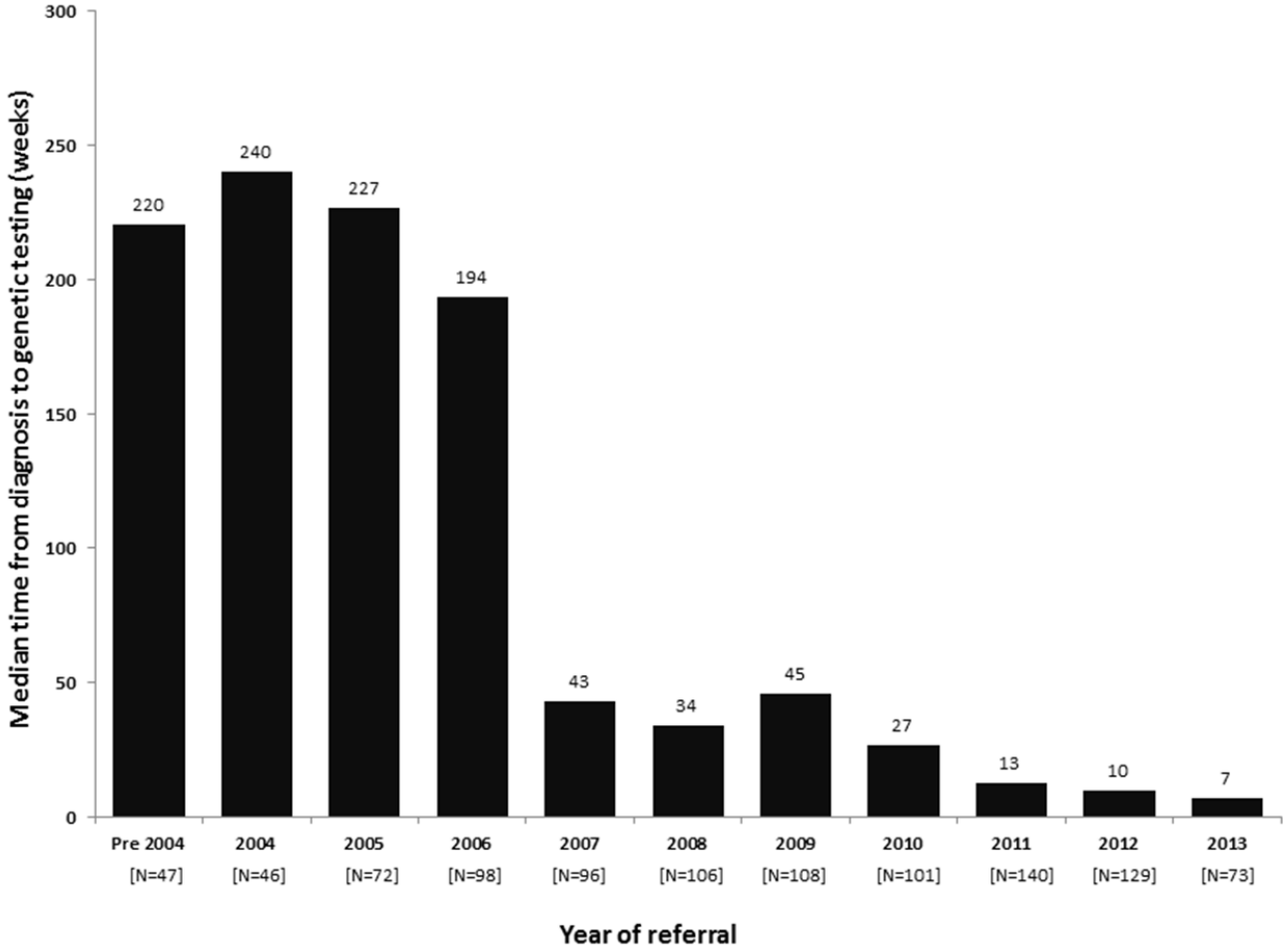
Supplementary Figure 1. Schematic representation of the neonatal diabetes cohort. Analysis of genetic aetiologies excluded patients for whom there was insufficient DNA for comprehensive testing (n=85).



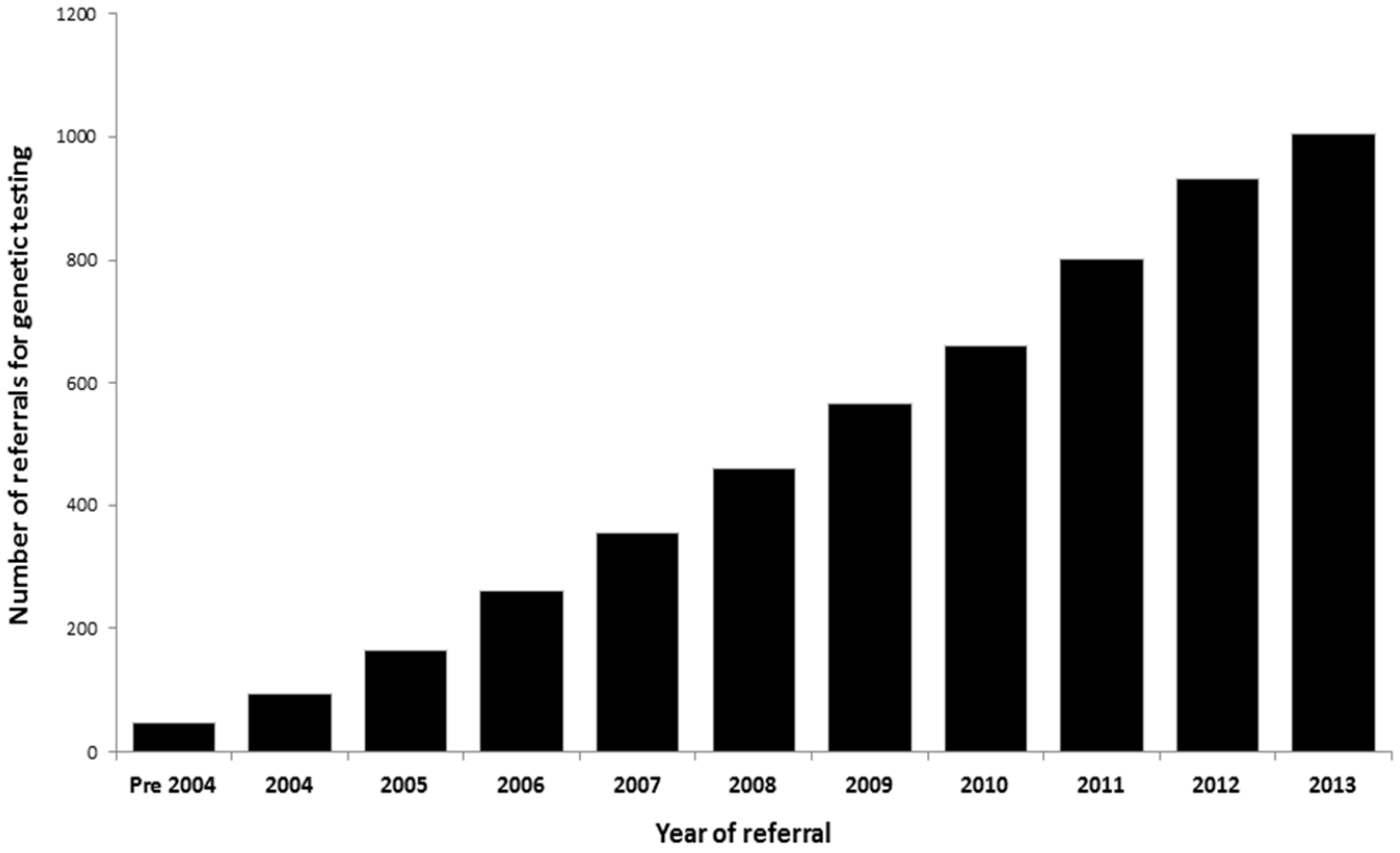
Supplementary Figure 2: Current genetic testing pipeline for neonatal diabetes referrals. Blue outline: diagnostic pipeline. Red outline: gene discovery pipeline



Supplementary Figure 3. Fall of the median time from diagnosis to referral for genetic testing over time. Bar chart representing the median time from clinical diagnosis of diabetes to referral for genetic testing between 01/01/2000 and 31/08/2013 (N=1016, age at diagnosis not available for N=4).



Supplementary Figure 4. Increase in the total number of referrals over time. Bar chart representing the cumulative number of worldwide referrals from 01/01/2000 to 31/08/2013 (N=1020).



Supplementary Table 1. List of countries with high prevalence (>20%) of consanguineous unions[1] and number of referrals for neonatal diabetes testing to the Exeter Molecular Genetics laboratory

Country	Number of neonatal diabetes referrals
Bahrain	2
Bangladesh	10
Egypt	9
India	75
Iran	2
Iraq	1
Israel	6
Jordan	16
Kuwait	8
Lebanon	2
Libya	6
Morocco	8
Oman	8
Pakistan	9
Qatar	1
Saudi Arabia	36
Sudan	8
Syria	1
Tunisia	1
Turkey	83
United Arab Emirates	14

Supplementary Table 2. Number and references for 253 patients included in the cohort who have been included in previous publications by the Exeter team.

Gene	N of patients tested in Exeter and previously published	References
ABCC8	41	2-13
EIF2AK3	27	3, 14-17
FOXP3	5	18
GATA4	4	19
GATA6	25	20-22
GCK	28	23
GLIS3	4	15, 24
HNF1B	1	25
IER3IP1	0	
INS	40	26-28
KCNJ11	50	3, 4, 7, 9, 29-43
MNX1	1	44
NEUROD1	2	45
NEUROG3	1	46
NKX2-2	2	44
PDX1	3	47
PTF1A	11	22, 48
RFX6	1	49
SLC19A2	2	50
SLC2A2	5	51
Total	253	

Supplementary Table 3. Genetic causes of neonatal diabetes identified in 840 neonatal diabetes patients.

Genetic cause	Mode on inheritance	Non consanguineous N (%)	Consanguineous N (%)
6q24		101 (12.8%)	12 (5.2%)
ABCC8	Dominant	112 (14.2%)	3 (1.3%)
	Recessive	22 (2.8%)	13 (5.7%)
EIF2AK3	Recessive	20 (2.5%)	56 (24.3%)
FOXP3	X-linked	11 (1.4%)	3 (1.3%)
GATA4	Dominant	3 (0.4%)	1 (0.4%)
GATA6	Dominant	29 (3.7%)	0 (0.0%)
GCK	Recessive	8 (1.0%)	22 (9.6%)
GLIS3	Recessive	3 (0.4%)	6 (2.6%)
HNF1B	Dominant	2 (0.3%)	0 (0.0%)
IER3IP1	Recessive	0 (0.0%)	1 (0.4%)
INS	Dominant	77 (9.7%)	6 (2.6%)
	Recessive	9 (1.1%)	18 (7.8%)
KCNJ11	Dominant	228 (28.9%)	12 (5.2%)
MNX1	Recessive	0 (0.0%)	1 (0.4%)
NEUROD1	Recessive	1 (0.1%)	2 (0.9%)
NEUROG3	Recessive	2 (0.3%)	0 (0.0%)
NKX2-2	Recessive	0 (0.0%)	2 (0.9%)
PDX1	Recessive	2 (0.3%)	4 (1.7%)
PTF1A	Recessive	3 (0.4%)	19 (8.3%)
RFX6	Recessive	0 (0.0%)	1 (0.4%)
SLC19A2	Recessive	2 (0.3%)	5 (2.2%)
SLC2A2	Recessive	2 (0.3%)	4 (1.7%)
ZFP57	Recessive	8 (1.0%)	4 (1.7%)
Unknown		145 (18.4%)	35 (15.2%)
Total		790	230

Supplementary Table 4. Summary of the clinical features associated with the 22 neonatal diabetes subtypes. * indicates features associated to specific mutations.

Genetic cause	Neonatal Diabetes Phenotype	Diabetes Treatment	Exocrine insufficiency needing replacement therapy	Additional Features	References
6q24	Transient	Insulin	No	Intrauterine growth retardation, macroglossia, umbilical hernia, neurological features (rare)	52-55 56
ABCC8	Transient, Permanent	Sulfonylureas	No	Developmental delay with/without epilepsy* (22% of cases)	12, 57 56
EIF2AK3	Permanent	Insulin	No	Skeletal dysplasia, liver dysfunction, developmental delay	17, 58
FOXP3	Permanent	Insulin	No	Eczema, enteropathy, other autoimmune features	59
GATA4	Transient, Permanent	Insulin	Yes*	Congenital heart malformation	19, 60
GATA6	Transient (rare), Permanent	Insulin	Yes	Congenital heart malformation, neurological defects, hypothyroidism, gut and hepato-biliary malformation	21, 22
GCK	Permanent	Insulin	No		61-67
GLIS3	Permanent	Insulin	No	Congenital hypothyroidism, renal cysts	24, 68, 69
HNF1B	Transient	Insulin	No	Pancreatic hypoplasia, renal cysts	25, 70
IER3IP1	Permanent	Insulin	No	Microcephaly, epilepsy	71-73
INS	Transient, Permanent	Insulin	No		27, 28 56
KCNJ11	Transient, Permanent	Sulfonylureas	No	Developmental delay with/without epilepsy* (29% of cases)	35, 36 56
MNX1	Permanent	Insulin	No	Sacral agenesis, neurological defects	44
NEUROD1	Permanent	Insulin	No	Cerebellar hypoplasia, sensorineural deafness, visual impairment	45
NEUROG3	Permanent	Insulin	No	Congenital malabsorptive diarrhea	46

NKX2-2	Permanent	Insulin	No	Severe neurodevelopmental defects	[44]
PDX1	Permanent	Insulin	Yes*		[47, 74-76]
PTF1A	Permanent	Insulin	Yes	Cerebellar agenesis*	[77, 78, 48]
RFX6	Permanent	Insulin	No	Intestinal atresia and/or malrotation, gall-bladder agenesis	[49, 79]
SLC19A2	Permanent	Thiamine	No	Thiamine-responsive megaloblastic anemia, sensorineural deafness	[50, 80-82]
SLC2A2	Transient	Insulin	No	Hepato-renal glycogen accumulation, renal dysfunction, impaired utilization of glucose and galactose	[51]
ZFP57	Transient	Insulin	No	Intrauterine growth retardation, neurological features (rare)	[83, 84]

Supplementary Methods

Samples were fragmented using a Bioruptor (Diagenode, Liège, Belgium), indexed for multiplexing and hybridised (in pools of 12 samples) according to the manufacturer's instructions. Sequencing was performed with an Illumina HiSeq 2000 (Illumina, San Diego, CA, USA) (48 samples per lane) and 100 bp paired end reads. The resulting reads were aligned with BWA and duplicates were removed with Picard. We then applied GATK indel realignment, and performed SNV and INDEL discovery and genotyping using GATK UnifiedGenotyper with standard hard filtering parameters according to GATK Best Practices recommendations[84]. Variants were annotated with ANNOVAR and pathogenic mutations located within 50 bp upstream and 50 bp downstream of each exon were identified.

As previously described[85], for the 21 genes for which testing is available in the Exeter laboratory by Sanger sequencing, the average depth of coverage was over 250 reads and >99% of bases had a minimum read depth of 30. Two specific regions of low coverage (<20 reads) were observed across two ~300bp GC-rich regions in the exon 2 of *GATA6* and *GATA4*. In patients for whom these regions were not sufficiently covered and no pathogenic mutation was identified, Sanger sequencing of the specific exon 2 amplicons were carried out in patients with congenital features suggestive of a *GATA6/GATA4* mutation (e.g. low birth weight, exocrine insufficiency, congenital heart malformation). Two positive controls (for a known heterozygous deletion and a known insertion) were included in each 48 sample batch to verify the ability to detect deletions/insertions.

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