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1 Monogenic diabetes

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27 **Abstract**

28

29 Monogenic diabetes includes several clinical conditions generally characterized by
30 early-onset diabetes, like neonatal diabetes, maturity-onset diabetes of the young
31 (MODY) and diabetes-associated syndromes. However, patients with apparent type
32 2 diabetes may actually have monogenic diabetes. Indeed, the same monogenic
33 diabetes gene depending of the functional impact of its variants can contribute to
34 different forms of diabetes with early or late onset. Same spectrum of diabetes
35 phenotypes can also be observed for a single specific pathogenic mutation shared by
36 different carriers, even of the same family. Monogenic diabetes is mostly due to
37 impaired function or development of pancreatic islets with defective insulin secretion
38 in absence of obesity. The most prevalent monogenic diabetes form is MODY that
39 may account for 0.5–5% of patients diagnosed with non-autoimmune diabetes, but is
40 probably underdiagnosed due to insufficient genetic testing. Most cases with
41 neonatal diabetes or MODY have an autosomal dominant form of diabetes. More
42 than 40 monogenic forms of diabetes have been identified so far, the most prevalent
43 being deficiencies for *GCK* (glucokinase) and *HNF1A* (hepatocyte nuclear factor 1
44 alpha). Some of these genes (including *GCK* and *HNF1A*) are actionable, namely
45 carriers of a pathogenic mutation should benefit from precision medicine. This
46 precision medicine includes specific treatments of hyperglycemia, the monitoring of
47 associated extrapancreatic phenotypes, and/or the follow up of clinical trajectories
48 especially during pregnancy, which increases patients' quality of life. Next-generation
49 sequencing has made affordable and cost efficient the genetic diagnosis of
50 monogenic diabetes that enables effective genomic diabetic medicine.

51 **Introduction**

52 Monogenic diabetes is a heterogeneous group of disorders that include various
53 clinical conditions associated with hyperglycemia, which are mostly due to impaired
54 function or altered development of islets of Langerhans (including pancreatic beta
55 cells that secrete insulin) and are linked to a single, pathogenic, genetic event.
56 Monogenic diabetes comprises a large spectrum of clinical conditions, such as
57 neonatal diabetes (a very rare form of monogenic diabetes at 1 in 90,000 live births
58 that occurs within the first 6 months of life), maturity-onset diabetes of the young
59 (MODY), an early-onset diabetes occurring during childhood, adolescence or young
60 adulthood (age of onset under 25 years according to the original definition) with
61 strong family history, and diabetes-associated syndromes (e.g. Wolfram syndrome,
62 Wolcott-Rallison syndrome and Mitchell-Riley Syndrome), the common denominator
63 of which is early-onset diabetes. Diabetes-associated syndromes are multisystem
64 diseases that cause neonatal diabetes or diabetes with a later onset¹. Diabetes may
65 be not recognized as a first manifestation of these syndromes¹.

66 The first gene identified to cause monogenic diabetes (*GCK*, encoding glucokinase, a
67 glucose sensor for the pancreas) was discovered in 1992^{2,3}. Since then, several
68 dozens of genes harboring rare, coding or even non-coding mutations causing
69 monogenic diabetes have been identified, following various modes of inheritance
70 (Table 1). Some of these genes are medically actionable, which means that
71 pathogenic mutations in these genes are related to health conditions with known
72 medical recommendations to act upon with the carriers (e.g. follow-up of clinical
73 trajectories, treatment of hyperglycemia). This advocates for an enhanced screening
74 for monogenic diabetes worldwide.

75 Monogenic diabetes phenotypes overlap with both type 1 and 2 diabetes mellitus,
76 and same genes can confer risk to a common form of diabetes or can cause
77 monogenic diabetes in another inherited context. Type 1 diabetes is due to
78 autoimmune beta-cell destruction, usually leading to absolute insulin deficiency, and
79 results from polygenic predisposition⁴. Mutations in several genes linked to
80 autoimmune diabetes have been found to cause monogenic diabetes (i.e. apparent
81 type 1 diabetes), mostly with a recessive pattern of inheritance (Figure 1). On the
82 other hand, type 2 diabetes is due to a progressive loss of adequate beta-cell insulin
83 secretion (i.e. mostly seen in adults) frequently on the background of insulin

84 resistance, and results from polygenic predisposition like type 1 diabetes⁴.
85 Nonetheless, the dominant deficiency of many genes causing monogenic diabetes
86 has been found in patients with apparent type 2 diabetes, namely with age of onset
87 above 40 years⁵. In fact, the diagnosis of type 2 diabetes can be referred as a
88 diagnosis of exclusion and therefore type 2 diabetes is very heterogeneous.
89 Research on monogenic diabetes has truly revolutionized our understanding of the
90 pathophysiology of diabetes and the genetics of common diseases⁶. Furthermore,
91 monogenic diabetes has provided one of the best examples of the vision of precision
92 medicine so far. This Primer focuses on monogenic forms of diabetes primarily due
93 to impaired function or development of pancreatic islets. It does not address potential
94 diabetes due to monogenic forms of insulin resistance such as lipodystrophy.

95 **Epidemiology**

96 MODY may account for about 2–5% of patients diagnosed with non-autoimmune
97 diabetes (as estimated in European patient cohorts, mainly from childhood diabetes
98 registries), with a global prevalence of ~100 per million in white European
99 populations⁷. However, the true prevalence of monogenic diabetes is still unknown. It
100 may be largely underestimated in many countries due to poor access to genetic
101 testing, no access to this diagnostic procedure or lack of awareness. In fact, genetic
102 testing is not widely available even in most affluent countries: for instance, it was
103 estimated that >80% of MODY cases in the United Kingdom (UK) may go
104 undiagnosed⁸. Hopefully, recent access in next-generation sequencing facilities has
105 improved MODY discovery rates at least in young patients with typical MODY clinical
106 features⁹. In the UK, the apparent prevalence of MODY is four times higher in South
107 West of England, where genetic testing is more widely implemented than in other UK
108 regions such as Northern Ireland where it is not the case⁸. It is unlikely that ethnic
109 differences explain these differences, but rather lower doctors' awareness of MODY
110 in some UK regions. In the general population from the United States, 3 in 200
111 individuals from the general population have been shown to carry a variant that has
112 been reported previously to cause MODY although the majority of them were not
113 known to have diabetes yet¹⁰.
114 A recent study in different countries around the Mediterranean Sea has screened for
115 pathogenic mutations in genes linked with monogenic diabetes in patients with an

116 early age of diagnosis: in the entire study population, a genetic diagnosis of
117 monogenic diabetes was established in 18% of the participants. In most countries,
118 the pathogenic mutations were mostly harboured by *GCK* (7%) and *HNF1A* (5%).
119 However, diagnosis rates differed widely by country of inclusion, with the highest
120 rates observed in Greece (40%), Algeria (30%) and France (28%), and the lowest in
121 Tunisia (8%) and Turkey (12%) while no variant of interest were found in the
122 Moroccan patients¹¹. Differences in ethnicity, but also in patients' ascertainment, may
123 explain this variability, knowing that the inclusion criterion was an age below 40 years
124 at diabetes diagnosis (without insulin treatment and obesity at diagnosis, and with no
125 autoantibodies to at least three islet cell antibody tests), or self-reported family history
126 of diabetes consistent with autosomal dominant inheritance.

127 Recently, a comprehensive genetic investigation in South India revealed a
128 monogenic etiology in 15% of the cases: however, in contrast to European
129 populations, the distribution of MODY genes was very different with a lack of
130 pathogenic mutations in *GCK*¹².

131 Although the true prevalence of monogenic diabetes is still unclear in adult patients
132 with history of early-onset diabetes and absence of obesity, its putative occurrence
133 among patients with typical type 2 diabetes (*i.e.* with age of onset > 40 years and
134 overweight or obesity) has been largely ignored until recently. In a recent study, 6%
135 of patients of European origin with apparent type 2 diabetes followed by a French
136 diabetes clinic were found to carry pathogenic mutations in genes linked to
137 monogenic diabetes⁵. These patients with MODY mutations were impossible to
138 identify using clinical criteria as they did not differ from other patients with T2D⁵.
139 Furthermore, among them, 2% carried pathogenic mutations in actionable MODY
140 genes (*i.e.* their discovery should lead to an attempt to change diabetes care)⁵. In
141 addition, in an Italian study, ~3% of adult patients with early-onset type 2 diabetes
142 carried pathogenic mutations in MODY genes¹³. This was in line with a recent study
143 done in US children with type 2 diabetes¹⁴. The main conclusion is that hidden
144 MODY exists among patients with apparent type 2 diabetes and only genetic
145 diagnosis can recognize them, and when possible can enable precision medicine.

146 **Mechanisms/pathophysiology**

147

148 Pancreatic islets, or islets of Langerhans, are islands of endocrine cells scattered
149 throughout the pancreas¹⁵. Human pancreatic islets include 60% beta cells that
150 produce insulin in response to a glucose challenge, 30% alpha cells that produce
151 glucagon, with the remainder 10% made up of delta cells (somatostatin-producing),
152 PP cells (pancreatic polypeptide-producing), and epsilon cells (ghrelin-producing)¹⁵.
153 Endocrine cells are randomly distributed in human islets¹⁵. In pancreatic beta cells,
154 insulin is packaged into secretory granules and released in response to high glucose
155 (and other nutrient) levels, neurotransmitters (that are released in response to food)
156 and incretin hormones¹⁵.

157 Many genes causing monogenic diabetes have been found via multiple genetic
158 strategies and technologies that have evolved according to the state-of-the-art in
159 genetics (Table 1; Box 1). MODY inheritance mostly follows an autosomal dominant
160 mode whereas neonatal diabetes and diabetes-associated syndromes can be
161 dominant or recessive disorders. Linkage analyses (mostly using microsatellites),
162 followed by Sanger sequencing of candidate genes in diabetes-associated linkage
163 genomic peaks were very successful in the discovery of various types of MODY (e.g.
164 dominant *GCK*-, *HNF1A*-, *HNF4A*- or *CEL*-diabetes)^{2,3,16-18}. In suspected recessive
165 forms of monogenic diabetes, linkage analyses were mostly based on the discovery
166 of runs of homozygosity (ROH), which are genomic regions where identical
167 haplotypes are inherited from each (consanguineous) parent. Surprisingly perhaps,
168 single candidate gene strategy (using Sanger sequencing), which requires a prior
169 functional hypothesis that particular genes of interest contain pathogenic mutations
170 that may cause monogenic diabetes, was also very successful. More recently, the
171 advent of next-generation sequencing technology (including whole-exome and
172 whole-genome sequencing) has enabled the discovery of new monogenic diabetes
173 genes. It is striking that the vast majority of monogenic diabetes genes are well
174 expressed in pancreatic islets and beta cells, and play an important role in the
175 development and/or function of pancreatic beta cells, notably insulin secretion (Table
176 2; Figure 2). In fact, all compartments of the pancreatic beta cells can be impacted in
177 monogenic diabetes. We are showing below the main genes causing monogenic
178 diabetes compartment by compartment.

179 **Nucleus**

180 A plethora of genes whose mutations cause monogenic diabetes encode
181 transcription factors that are highly expressed in pancreatic islets and beta cells.
182 Among these, the most frequently mutated is *HNF1A*, whose deficiency leads to
183 MODY or even to adult-onset non-autoimmune diabetes. *HNF1A* is mainly expressed
184 in pancreatic beta cells and in hepatocytes. Pathogenic mutations in this gene lead to
185 impaired transactivation function, protein expression, DNA binding, and/or subcellular
186 (nuclear) localization¹⁹. *HNF1A* is an important transcription factor for the
187 maintenance of beta-cell function, as well as for the development and maturation of
188 pancreatic islets²⁰. *HNF1A* directly binds to the promoter region of the insulin gene
189 *INS*, positively regulating the transactivation of the latter²⁰. Importantly, the bi-allelic
190 deficiency of *PDX1* or *PTF1A*, and the dominant deficiency of *GATA6* cause neonatal
191 diabetes linked with pancreatic agenesis, along with a spectrum of extrapancreatic
192 features. However, penetrance can be incomplete²¹. *PDX1*, *PTF1A* and *GATA6* are
193 transcription factors that play a key role in pancreatic development and pancreatic
194 cell fate specification^{22–24}. Notably, *PTF1A* does not seem to be expressed in adult
195 and fetal pancreatic beta cells; however, it is expressed in the very early stages of
196 pancreatic development, being required for pancreatic specification and exocrine
197 *versus* endocrine fate decision²³.

198 **Endoplasmic reticulum**

199 Several monogenic diabetes genes (*i.e.* *WFS1*, *CISD2*, *MIA3* [previously called
200 *TANGO1*], *MANF*, *YIPF5*, *DNAJC3*, *EIF2AK3*, *EIF2B1*, *PPP1R15B* and *IER3IP1*;
201 **Table 1**) encode proteins that play a key role in endoplasmic reticulum, in particular
202 in the maintenance of endoplasmic calcium homeostasis (**Figure 2**). Strikingly, all
203 these genes are ubiquitously expressed and their bi-allelic deficiency systematically
204 causes severe early-onset diabetes associated with extrapancreatic features
205 including deafness, hearing loss, renal tract abnormalities, short stature, hepatic
206 dysfunction, microcephaly, epilepsy and other neurodevelopmental disorders. It has
207 been shown that the deficiency of these genes results in endoplasmic reticulum
208 stress indicative of increased unfolded protein response (UPR) signaling, leading to
209 insulin secretion failure or even apoptosis of pancreatic beta cells^{25,26}. Recent
210 studies (focused on the deficiency of *YIPF5* and *MIA3*) have also suggested that
211 endoplasmic reticulum stress may be caused by impaired transport from the
212 endoplasmic reticulum through the Golgi apparatus²⁶.

213 **Plasma membrane**

214 Several monogenic diabetes genes encode channel subunits (*ABCC8*, *KCNJ11*, and
215 *KCNK16*) or transporters (*SLC2A2*, *SLC19A2*) that are embedded in the plasma
216 membrane (Figure 2). *ABCC8* and *KCNJ11* encode the subunits of an ATP-sensitive
217 potassium channel that are highly expressed in the pancreatic islets and beta cells,
218 although their expression is also high in other organs and tissues such as the
219 cerebellum and pituitary (Table 2). The ATP-sensitive potassium channel encoded by
220 *KCNJ11* and *ABCC8* plays a key role in insulin granule exocytosis from pancreatic
221 beta cells. Indeed, an increase in glucose metabolism leads to an increase in
222 intracellular ATP/ADP ratio due to enhanced glycolysis and Krebs cycle activity,
223 which in turn results in closure of the ATP-sensitive potassium channel and
224 membrane depolarization⁷. This activates voltage-dependent calcium channels
225 leading to a rise in intracellular calcium, which stimulates insulin release. Activating
226 (or gain-of-function) homozygous or heterozygous mutations in *ABCC8* or *KCNJ11*
227 lead to neonatal diabetes, MODY or even late-onset diabetes, since the mutated
228 ATP-sensitive potassium channel remains open despite high glucose levels, thereby
229 leading to inhibition of insulin secretion in mutation carriers⁷. An activating mutation in
230 *KCNK16* encoding another potassium channel has recently been suggested to cause
231 MODY²⁷. Contrary to *ABCC8* and *KCNJ11*, the expression of this gene is specific to
232 pancreatic beta cells. A pathogenic mutation in this gene was found to cause a
233 profound increase in potassium current, altering beta-cell calcium flux, and
234 decreasing glucose-stimulated insulin secretion²⁷. Very rare forms of monogenic
235 diabetes were attributed to pathogenic mutations in *SLC2A2* and *SLC19A2* encoding
236 glucose and thiamine transporters^{28,29}. Recessive *SLC2A2*- and *SLC19A2*-diabetes
237 (known as Fanconi-Bickel syndrome and Rogers syndrome, respectively) lead to
238 severe extrapancreatic features including failure to thrive, hepatomegaly secondary
239 to glycogen accumulation, galactose intolerance, proximal tubular nephropathy,
240 phosphaturia, aminoaciduria and hypophosphatemia for *SLC2A2* deficiency, and
241 megaloblastic anaemia, and sensorineural deafness for *SLC19A2* deficiency^{28,29}.
242 Isolated early-onset diabetes was also reported in dominant-*SLC19A2* deficiency³⁰.

243 **Mitochondria**

244 The mitochondrial m.3243A>G mutation is one of the most frequent point mutations
245 of the mitochondrial DNA³¹. This mutation causes a syndrome known as MELAS for

246 Mitochondrial Encephalopathy with Lactic Acidosis and Stroke-like episodes, or
247 MIDD for Maternally-Inherited Diabetes and Deafness. This mutation can actually
248 lead to a broad spectrum of phenotypes more or less severe, including hearing loss,
249 diabetes, seizure, stroke-like episodes, muscle weakness and heart disease³¹. The
250 molecular mechanisms underlying m.3243A>G-associated phenotypes may be due
251 to a complex interplay between m.3243A>G mutant load, mitochondrial DNA copy
252 number, nuclear genetic factors, epigenetics, and environmental exposures³².

253 **[H2] Cytosol**

254 In the cytosol, the most commonly mutated gene in dominant monogenic diabetes is
255 *GCK* encoding glucokinase, which is the predominant glucose-phosphorylating
256 enzyme in pancreatic beta cells and in hepatocytes³³. *GCK* has a relatively low
257 affinity for glucose and displays positive cooperativity for this substrate, despite the
258 fact that it is a monomeric enzyme³³. Functional analyses of the kinetic properties of
259 the *GCK* mutants found in MODY have shown that the relative enzymatic activity was
260 impaired, leading to a decrease in the glycolytic flux in pancreatic beta cells³³. This
261 translates *in vivo* as a glucose-sensing defect and a right shift in the dose response
262 curve of glucose-induced insulin secretion³³. *GCK* mutations are pathogenic through
263 different mechanisms including impaired enzymatic activity, altered protein stability
264 and/or increased interaction with the glucokinase regulatory protein^{34,35}. In the liver, a
265 decrease in glycogen synthesis and storage, and an increase in gluconeogenesis
266 after standard meals were reported in patients deficient for *GCK*; contributing to
267 postprandial hyperglycemia³³. Pathogenic homozygous mutations in *GCK* also cause
268 neonatal diabetes³⁶.

269 **Insulin granules**

270 Dominant or bi-allelic pathogenic mutations in *INS* were found to cause “neonatal”
271 diabetes, (usually in infancy rather than in the first months of life), MODY or even
272 late-onset diabetes. Most of the pathogenic, coding *INS* mutations described so far
273 have been shown to cause severe proinsulin misfolding, endoplasmic reticulum
274 retention, increased UPR signaling and pancreatic beta-cell apoptosis³⁷.
275 Homozygous, pathogenic, non-coding *INS* mutations were reported in patients with
276 neonatal diabetes^{38,39}. These mutations decreased insulin biosynthesis through
277 distinct mechanisms, including *INS* gene deletion, severe dysfunction of
278 transcriptional activity due to mutations located in the *INS* promoter, lack of the

279 translation initiation signal, and altered mRNA stability because of the disruption of a
280 polyadenylation signal^{38,39}.

281 **Exocrine pancreas**

282 A dominantly inherited monogenic form of diabetes is caused by mutations in *CEL*
283 encoding the carboxyl ester lipase, which is expressed by pancreatic acinar cells^{18,40}.
284 Patients with a pathogenic *CEL* mutation develop childhood-onset exocrine pancreas
285 dysfunction followed by diabetes during adulthood. Clinical investigations have
286 reported that pre-diabetic mutation carriers exhibit significantly reduced first-phase
287 insulin response with early β -cell dysfunction prior to development of diabetes¹⁸.
288 However, it is unclear how *CEL* mutations cause diabetes. Studies with *in vitro* and *in*
289 *vivo* human pluripotent stem cell-based disease models and pancreatic cell lines
290 have demonstrated co-localization of insulin and CEL protein in mutant beta-like
291 cells, which supports a crosstalk between exocrine and endocrine compartments⁴¹.
292 The presence of the mutant CEL in insulin-expressing cells from patients with this
293 form of diabetes provides further evidence that an abnormal relationship between
294 pancreatic exocrine and endocrine cells likely underlies the beta-cell dysfunction in
295 this form of diabetes⁴¹. Specifically, the mutant CEL protein is taken up and remained
296 insoluble in beta cells with consequent development of endoplasmic reticulum stress
297 that contributes to defects in secretory function and proliferation^{40,41}. Whether CEL is
298 taken up by beta cells through a paracrine or endocrine pathway within the pancreas
299 and if circulating CEL in human plasma is preferentially taken up by beta cells
300 compared to other cell types requires further investigation.

301 **Diagnosis, screening and prevention**

302 **Clinical presentation**

303 According to its original definition, MODY is inherited following an autosomal
304 dominant pattern (*i.e.* 50% of offspring are carriers of heterozygous, pathogenic DNA
305 mutations and are in theory affected) and occurs in lean individuals before the age of
306 25 years who do not always need insulin therapy⁴². Hyperglycemia and related
307 symptoms can be mild especially at disease onset and can deteriorate with
308 increasing disease duration, depending on the gene and the nature of the mutations
309 causing hyperglycemia^{7,43}.

310 In practice, MODY should be strongly suspected in children and young adults with
311 mild hyperglycemia at onset in the absence of typical features of both type 1 and type
312 2 diabetes. The former includes the coexistence of autoimmunity and the need of
313 insulin treatment at diagnosis (possibly presenting with ketoacidosis), while obesity
314 and other features related to insulin resistance including acanthosis nigricans, and
315 sometimes early-onset atherogenic dyslipidemia and essential hypertension are
316 among the latter^{6,7,33,44}. Finally, although the possibility of a *de novo* mutation should
317 always be considered, a strong family history of diabetes reinforces the suspicion of
318 MODY. While these criteria are valid, they are far from exhaustive. Indeed, several
319 reports have now made it clear that the picture is much more heterogeneous, with
320 MODY also occurring in patients (both children and adults) with excess adiposity and
321 other features of insulin resistance and/or in middle-aged individuals^{7,45}. As a
322 consequence, the “old definition”⁴² misses at least a quarter of patients with MODY
323 and therefore should be abandoned^{8,46,47}.

324 The marked heterogeneity in the clinical presentation of MODY is largely the
325 consequence of the multiple genetic etiologies of this form of diabetes. However,
326 pathogenic, heterozygous mutations in several genes, including *ABCC8*, *KCNJ11*,
327 *INS*, *HNF1B*, *GATA4* and *GATA6*, are involved in MODY but also in severe cases of
328 neonatal diabetes (Table 1); at the same time, rare and frequent variants in some of
329 these genes also contribute to shaping the risk for common multifactorial type 2
330 diabetes. Thus, the different forms non-autoimmune diabetes belongs to a
331 continuous spectrum of disease rather than being distinct entities^{6,48}. In fact, it has
332 been shown that, even in the same family, the same heterozygous mutation can lead
333 to neonatal diabetes, MODY, late-onset non-autoimmune diabetes or even normal
334 glucose tolerance at an advanced age^{21,49–51}, an observation that clearly highlights
335 the incomplete penetrance of pathogenic mutations in monogenic diabetes. Notably,
336 a high polygenic risk score, summarizing the effect of several hundred genetic
337 variants associated with type 2 diabetes, was found to be a significant determinant of
338 an earlier age of diabetes diagnosis in patients with a pathogenic mutation of
339 *HNF1A*⁵¹. Therefore, the polygenic background (as captured by a polygenic risk
340 score for common type 2 diabetes) could be one of the causes of this variable
341 penetrance of rare, pathogenic mutations in monogenic diabetes.

342 Furthermore, very recently, it was reported that approximately 20% of the pathogenic
343 mutations found in patients indicated as having MODY were actually harbored by

344 genes or loci typically associated with syndromic presentations; these particularly
345 include the (i) maternally inherited mitochondrial m.3243A>G variant, (ii)
346 heterozygous, pathogenic mutations in *HNF1B* and (iii) bi-allelic, pathogenic
347 mutations in *WFS1*^{44,52,53}. These observations challenge the concept of MODY and
348 diabetes-associated syndromes being distinct clinical entities. It is now clear that
349 MODY (especially due to *WFS1*, *SLC19A2* and *GCK* deficits) without any atypical
350 presentation can be recessively inherited (*i.e.* with homozygous mutations or
351 compound heterozygous pathogenic variants), especially but not exclusively in
352 population with high rates of consanguinity⁵⁴. As mentioned above, these new
353 findings are likely the consequences of the variable penetrance and expressivity of
354 mutations in genes causing monogenic diabetes and further support the existence of
355 a continuous spectrum of disease, with very blurred boundaries between each of the
356 different diabetes subtypes thus far described as distinct entities^{45,55}.
357 All this indicates the need to reconsider the current classification of monogenic
358 diabetes which appears to be too rigid and inconsistent with both clinical and
359 molecular evidence. A practical proposal is to group the various forms of diabetes
360 due to genetic mutations under the deliberately generic umbrella of “monogenic
361 diabetes”, to which the following notations are added consistently with each specific
362 case: (i) the disease-causing gene; (ii) the type of hereditary transmission (*e.g.*
363 dominant, recessive) and (iii) the peculiar features of clinical presentation (*e.g.*
364 neonatal onset of hyperglycemia, presence of syndromic features). For example,
365 MODY due to pathogenic, heterozygous mutations in *GCK* would be “dominant *GCK*-
366 diabetes” while neonatal hyperglycemia due to pathogenic, homozygous mutations in
367 *GCK* would be “recessive, neonatal, *GCK*-diabetes”. As an additional example,
368 diabetes due to pathogenic, heterozygous mutations in *HNF1B* would be defined as
369 “dominant *HNF1B*-diabetes” or “dominant, syndromic *HNF1B*-diabetes” depending
370 on the absence or presence of renal, urinary, genital or gonadal abnormalities.

371 **Identification of patients for genetic screening**

372 The traditional approach to identifying candidates for MODY genetic screening
373 utilized the original clinical criteria for diagnosis⁴². However, these criteria are neither
374 sensitive nor specific enough for identifying the majority of individuals with
375 monogenic forms of diabetes. Large cases series have shown that in some
376 populations pathogenic mutations are found in only 10% of all individuals suspected

377 to have MODY by clinical criteria (e.g. early-onset non-autoimmune diabetes with
378 normal weight)^{12,56}. Subsequently, attempts were made to further refine the diagnosis
379 of MODY using a risk calculator, mainly developed in populations of European origin.
380 This MODY risk calculator, utilizing variables such as current age, age at diagnosis,
381 gender, ongoing treatment, duration of insulin treatment, family history of diabetes,
382 body mass index, and glycated hemoglobin A1c (HbA1c) levels⁵⁷, tend to perform
383 well in distinguishing individuals with MODY from those with type 1 diabetes.
384 However, they are less useful in differentiating MODY from type 2 diabetes,
385 particularly in populations (e.g. South Asian) with a high prevalence of youth-onset
386 type 2 diabetes⁵⁸.

387 Considering the limitations of available diagnostic criteria and risk scores, and the
388 fact that universal genetic screening of all youth-onset diabetes is unfortunately
389 impractical in large parts of the world, the identification of candidates for screening is
390 best achieved using a combination of phenotypic and biochemical variables. There is
391 some evidence, albeit based on models with inherent assumptions, that a phenotype-
392 based screening strategy for monogenic diabetes is cost-effective⁵⁹; however, this
393 needs confirmation with larger studies.

394 **Patient age**

395 Diabetes diagnosed within the first 6 months of life is most likely due to monogenic
396 defects, as autoimmune type 1 diabetes is rare at this age⁶⁰. More than 50% of
397 children with neonatal diabetes have been found to carry pathogenic mutations in
398 *ABCC8*, *KCNJ11* or *INS*^{60,61}. Diabetes due to these mutations is mostly diagnosed
399 within the first 6 months, although it can occasionally present beyond 6 months⁶⁰.
400 Diabetes due to pathogenic mutations in *HNF1A* and *HNF4A* tend to present with
401 hyperglycemia before the age of 25 years, although the penetrance of disease by this
402 age is only around 60%⁶². Individuals with dominant *GCK*-diabetes may be
403 diagnosed at any age, and depending on this, may be treated as type 1 diabetes,
404 type 2 diabetes or even gestational diabetes. The phenotype of nonprogressive
405 hyperglycemia in these cases only becomes apparent with the passage of time. They
406 are not at risk of developing chronic complications of diabetes⁴³.

407 **Family history of diabetes**

408 According to the originally described clinical criteria, MODY is characterised by
409 severe young-onset diabetes and a positive family history of young-onset diabetes in

410 several consecutive generations. However, the majority of patients with type 2
411 diabetes will also report a positive family history of diabetes in either or both
412 parents¹³. Even so, a family history of non-insulin treated young onset diabetes in an
413 individual diagnosed with type 1 diabetes should raise the suspicion of monogenic
414 diabetes.

415 **Obesity and markers of insulin resistance**

416 Presence of overweight or obesity, and markers of insulin resistance (e.g. acanthosis
417 nigricans and skin tags) would suggest a diagnosis of type 2 diabetes rather than
418 monogenic diabetes in such cases. It should, however, be noted that type 2 diabetes
419 can occur even in the absence of obesity or clinically evident insulin resistance,
420 particularly in ethnic groups such as South Asians.

421 **Presence of extrapancreatic features**

422 Presence of multi-organ involvement (e.g. renal cysts in dominant *HNF1B*-diabetes;
423 hepatic, renal and skeletal abnormalities in Wolcott-Rallison syndrome; deafness,
424 optic atrophy, diabetes insipidus and genitourinary abnormalities in Wolfram
425 syndrome; deafness and megaloblastic anemia in Rogers' syndrome) should prompt
426 genetic testing for elucidation of the molecular defect. Most of these syndromic forms
427 of diabetes are due to bi-allelic, pathogenic mutations (in *EIF2AK3* [Wolcott-Rallison
428 syndrome], *WFS1/CISD2* [Wolfram syndrome] and *SLC19A2* [Rogers' syndrome]
429 genes, respectively) but also heterozygous, pathogenic mutations in *HNF1B* (Table
430 1). As diabetes may be the first manifestation of many of these syndromes and may
431 remain the only manifestation for a considerable period of time⁵³, it is important to
432 look for mutations in syndromic diabetes genes in all patients with suspected
433 monogenic diabetes⁴⁴. On the contrary, extra pancreatic features such as kidney
434 failure and pancreatic exocrine dysfunction may precede diabetes by decades in
435 dominant *HNF1B*-diabetes and dominant *CEL*-diabetes, respectively^{18,63}.

436 **Biochemical variables**

437 Absence of islet autoantibodies, presence of endogenous insulin production (as
438 evidenced by detectable C-peptide levels distant from the time of diagnosis) and
439 modestly elevated blood glucose levels have been suggested as criteria for selection
440 of individuals for genetic testing^{47,64–66}. However, another study concluded that no
441 single clinical criterion was able to identify all patients with monogenic diabetes⁶⁷. It

442 should also be noted that while these criteria have been shown to perform well in
443 distinguishing monogenic diabetes from type 1 diabetes, they are unlikely to reliably
444 distinguish monogenic diabetes from type 2 diabetes. Some studies have even
445 suggested that offering genetic screening for MODY could be considered for all
446 children with diabetes irrespective of other clinical characteristics⁶⁸. This approach,
447 however, is not practical in resource-constrained settings.

448

449 Some clinical pointers to differentiate between monogenic diabetes and the more
450 common type 1 and type 2 diabetes are given in **Figure 3**.

451 **Genetic screening for monogenic diabetes**

452 In the candidates described above, genetic screening for monogenic diabetes is
453 carried out by sequencing the coding parts of genes known to be involved in this
454 disease. In the 2000s and even before, this screening was performed via Sanger
455 sequencing which was very labor-intensive and expensive. Since the advent of next-
456 generation sequencing, genetic screening for monogenic diabetes has become
457 increasingly cost-effective and less laborious. In this context, two sequencing
458 technologies are mostly used today in genetic diagnostic laboratories: (i) targeted
459 enrichment of a set of genes (or gene panels) known to be involved in monogenic
460 diabetes; and (ii) whole-exome sequencing (*i.e.* sequencing of ~2 % coding part of
461 the genome). Thanks to their targeted nature, gene panels inherently lead to a
462 smaller amount of data to handle and lower cost, and decrease the risk of secondary
463 findings when compared to whole-exome sequencing^{69,70}. However, as new genes
464 are discovered, the gene panel must be re-designed and re-validated. This is not
465 necessary with whole-exome sequencing. Also, while whole-exome sequencing
466 leads to bioinformatic challenges resulting from the large amount of data, it enables
467 the identification of pathogenic variants in genes that were not considered at
468 prescription (*i.e.* years after the initial assessment) and it fuels research of new
469 monogenic diabetes genes. Gene panels and whole-exome sequencing are both
470 limited in their capacity to detect copy-number variations (*e.g.* the deletion of one or
471 several entire exons which are common in dominant *HNF1B*-diabetes) or low-level
472 heteroplasmic mitochondrial variants (*e.g.* m.3243A>G variant causing monogenic
473 diabetes)^{69,71}. Therefore, multiplex ligation-dependent probe amplification (MLPA)
474 and Sanger sequencing of mitochondrial DNA are often used to supplement these

475 techniques^{69,71}. It is likely that whole-genome sequencing will substitute these
476 technologies in the next five years, although the issues of cost and large amount of
477 data need to be solved.

478 Since 2015, the standards and guidelines of the American College of Medical
479 Genetics and Genomics (ACMG) have enabled a rigorous interpretation of sequence
480 variants, which have been followed by all genetic diagnostic laboratories worldwide⁷².
481 These criteria use various types of variant evidence including population data (e.g.
482 extremely low frequency of variants in the Genome Aggregation Database),
483 computational data (e.g. use of *in silico* predictive programs of variants), functional
484 data (by *in vitro* or *in vivo* assays), and segregation data⁷². More specific guidelines
485 have been gathered by the ClinGen Monogenic Diabetes Expert Panel VCEP for
486 interpreting mutat. In dominant monogenic diabetes, it has recently been
487 recommended to exclude *BLK*, *KLF11* and *PAX4* from monogenic diabetes testing as
488 the evidence in support of these gene-disease associations is still controversial;
489 furthermore, it was recommended that all variants with a frequency higher than 0.001
490 in any ancestry included in the Genome Aggregation Database should be excluded
491 from the analysis⁷³.

492 **Prevention of monogenic diabetes**

493 Prevention in the classical sense of the term is not possible for monogenic diabetes
494 at present. The identification of a pathogenic mutation early in life give the
495 opportunity of diets low on fast acting carbohydrates. That may delay the onset of
496 diabetes and hence lower risk for diabetes-associated late complications. It is indeed
497 likely that environmental influences might play a role in the development of diabetes
498 in many of these cases. For instance, an individual harbouring a mutation in *HNF1A*
499 (involved in pancreas development) might develop diabetes at an earlier age (and
500 therefore be at higher risk of complications) if the beta cell reserve is placed under
501 strain by the development of obesity and insulin resistance. Correction of these
502 environmental factors might favourably modify the presentation of monogenic
503 diabetes at least in some cases. No studies looking at this issue have been reported
504 to our knowledge.

505 **Management**

506 The optimal treatment of young patients with emerging MODY has been discussed
507 since the 1970s⁷⁴. In 1991, one year before the discovery of *GCK* deficiency in
508 MODY, it was noted that MODY was very heterogeneous with some patients
509 responding well to sulfonylureas (*i.e.* the only diabetes treatment along with insulin
510 therapy in the USA at that time) and others not⁷⁵. It remains, that at that time nearly
511 all children discovered worldwide with hyperglycemia were immediately treated with
512 insulin by pediatricians. That included the numerous children that carried pathogenic
513 mutations in *GCK* who were mistakenly treated with daily injections of insulin with
514 poor results³.

515 Progressively, the recognition of MODY as an entity different from type 1 diabetes
516 and the identification of subtypes of MODY and other monogenic forms of diabetes
517 has led to a better understanding of monogenic diabetes pathophysiology and
518 elucidated clinical characteristics and trajectory of patients with monogenic diabetes.
519 From this point, specific treatments based on the nature of the genetic defect have
520 emerged and have been progressively introduced as the genetic diagnosis of
521 monogenic diabetes became more popular among the diabetes community (Figure
522 4). Given the outstanding efficiency of this personalized treatment, monogenic
523 diabetes can be seen as a one-of-a-kind achievement of precision medicine that is
524 only limited by the lack of provider knowledge of genetics and consequent lack of
525 availability of genetic counseling and testing in many territories.

526 **Dominant *GCK*-diabetes**

527 Dominant *GCK*-diabetes is characterized by sustained and non-manageable modest
528 fasting and post prandial hyperglycemia, which occurs in the very first years of life
529 and is actually only modulated by age. Indeed, it is not rare that elderly patients
530 deficient for *GCK* show HbA1c (*i.e.* a metric that reflects glucose control in the last
531 couple of months) higher than 7.5%, which is above the HbA1c targets of an optimal
532 diabetes treatment⁴³. This has led to an avalanche of non-useful medications given to
533 these patients in absence of genetic diagnosis, which are expensive and with
534 potential adverse effects.

535 Diabetes treatment in patients deficient for *GCK* is unnecessary for two reasons.
536 First, in these patients, no treatment can modify blood glucose that is firmly controlled
537 by *GCK* enzymatic activity. Second, it has been unambiguously demonstrated that
538 these patients do not develop any typical complications of diabetes (*e.g.* retinopathy,

539 nephropathy)⁴³; thus, there is no reason to manage a form of diabetes that is not
540 harmful for health. Remarkably, discontinuation of diabetes treatment does not
541 change glucose homeostasis or other medical outcomes of these patients, whatever
542 the duration of the condition before genetic recognition⁷⁶. Asymptomatic, mild fasting
543 hyperglycaemia (usually 5.6–8.0 mmol/l) related to dominant *GCK*-diabetes should
544 be only monitored without any attempt to fix it. However, dominant *GCK*-diabetes
545 should be taken seriously in the management of pregnancies.

546 Indeed, when a mother with diabetes carries a pathogenic *GCK* mutation while the
547 fetus does not carry the mutation, maternal hyperglycemia causes fetal
548 hyperinsulinemia and increased risk of macrosomia⁷⁷. On the contrary, when the
549 mother and her fetus share the same pathogenic *GCK* mutation, the glucose
550 threshold to trigger insulin secretion is similar in the mother and her fetus, leading to
551 normal fetal insulin levels and average birth weight⁷⁷. Furthermore, if the mother
552 presents with normal blood glucose levels and the father carries a pathogenic *GCK*
553 mutation that was transmitted to the fetus, maternal blood glucose levels are
554 insufficient to stimulate adequate fetal insulin secretion to sustain optimal growth,
555 leading to increased risk of low birth weight⁷⁸. Finally, if the mother presents with
556 normal blood glucose levels and the father carries a pathogenic *GCK* mutation that
557 was not transmitted to the fetus, fetal insulin secretion and birth weight are normal⁷⁷.
558 Therefore, insulin therapy should be given to a pregnant woman deficient for *GCK*
559 only when frank hyperglycemia occurs and/or when diagnostic ultrasonography
560 shows accelerated fetal growth (as elevated fetal insulin secretion leads to increased
561 risk of fetal macrosomia and associated obstetric complications)⁷. In fact, it would be
562 important to diagnose dominant *GCK*-diabetes in all women with gestational diabetes
563 (which is rarely done unfortunately), as the optimal diabetes care greatly depends on
564 whether the fetus has inherited the pathogenic *GCK* mutation or not, rather than the
565 degree of maternal blood glucose. It has been stated that around 5% of women with
566 gestational diabetes carry a pathogenic mutation causing MODY (and not only in
567 *GCK*)⁷⁹, but actually no large genetic study of women with GDM has systematically
568 addressed this issue yet.

569 Dominant *GCK*-diabetes should be considered in pregnant women with mild fasting
570 hyperglycemia (5.6–8.0 mmol/L), often during the first trimester, and with normal
571 body mass index. If fasting hyperglycemia is found in the second trimester, MODY
572 might be suspected in case abnormal 120-min oral glucose tolerance test above 7.5

573 mmol/l with HbA1c being either normal or moderately increased (5.6–7.6%). These
574 patients usually present with a history of gestational diabetes in a previous
575 pregnancy, a record of mild hyperglycemia before conception or after the delivery
576 and a strong family history of type 2 diabetes at early ages. It is also possible to
577 suspect dominant *GCK*-diabetes with history of fetal macrosomia in previous
578 pregnancies, or of insulin therapy only during the previous pregnancy that has been
579 removed after delivery⁷⁹.

580 **Dominant *HNF1A*- or *HNF4A*-diabetes**

581 *HNF4A* and *HNF1A* encode two key transcription factors for insulin secretion control.
582 Dominant *HNF1A*- or *HNF4A*-diabetes often causes severe, early-onset diabetes,
583 which is frequently revealed at puberty (*i.e.* when insulin resistance can appear)³³. In
584 absence of genetic diagnosis, patients deficient for *HNF4A* or *HNF1A* are
585 unfortunately generally treated by insulin injections⁷. If glucose homeostasis is badly
586 controlled, dominant *HNF1A*- or *HNF4A*-diabetes shares the same long-term risks as
587 type 1 diabetes, namely diabetic kidney disease and retinal complications. However,
588 as both *HNF4A* and *HNF1A* modulate the liver metabolism of sulfonylureas, the
589 intake of oral sulfonylureas has been shown to be particularly efficient at low dosage
590 in the patients deficient for *HNF4A* or *HNF1A*, which diminishes the risk of
591 hypoglycemia⁸⁰. These two forms of monogenic diabetes are thus optimally treated
592 with low-dose sulfonylureas because of their increased insulin secretion and their
593 increased insulin sensitivity.

594 Unfortunately, as the genetic diagnosis is often much delayed in age, the current
595 practice is still to introduce oral sulfonylureas after decades of insulin therapy,
596 especially when diabetes occurs in adolescence or young adulthood and is confused
597 with type 1 diabetes. This is tragic as it is important to perform the switch from insulin
598 to sulfonylureas as early as possible. Indeed, at any age, the successful switch of
599 insulin therapy into sulfonylureas in patients deficient for *HNF1A* or *HNF4A* is highly
600 dependent of the residual insulin secretion that can be measured by the C-peptide
601 which is the residue of the processing of proinsulin to insulin, reflecting insulin
602 endogenous production⁸¹. Furthermore, body mass index, disease duration and
603 HbA1c levels help predict the efficacy of sulfonylureas in patients deficient for *HNF1A*
604 or *HNF4A*⁷⁶. As insulin secretion progressively declines in these patients, it is of
605 paramount importance to recognize these conditions as early as possible. When the

606 treatment with sulfonylureas is not sufficiently efficient, it has been proposed to treat
607 these patients with glucagon-like peptide 1 (GLP1) analogs that may work well
608 according to recent studies⁸².

609 With regard to pregnancy, fetal growth is affected by maternal glycemic control in
610 dominant *HNF1A*-diabetes, and by both fetal mutation status and maternal
611 hyperglycemia in dominant *HNF4A*-diabetes⁷⁹. Importantly, sulfonylureas cross the
612 placental barrier and can lead to macrosomia and hyperinsulinemic hypoglycemia,
613 particularly in the third trimester⁷⁹. Therefore, it is recommended to switch to insulin
614 at pre-pregnancy (when possible) or to switch to insulin at the end of the first
615 trimester if the glucose control is adequate during the first months of pregnancy. The
616 overall principles of insulin treatment in these pregnant women with dominant
617 *HNF1A*- or *HNF4A*-diabetes are actually similar to the treatment of other pregnant
618 women with diabetes. However, due to the risk of higher birth weight and fetal
619 macrosomia, the pregnancy of these women should be regularly monitored by
620 sonography to detect the fetal growth since 28th week of gestation every two weeks⁷⁹.
621 If macrosomia is identified, induction of delivery or caesarian between 35 and 38th
622 week of gestation should be considered⁷⁹.

623 Importantly, dominant *HNF1A*-diabetes can be associated with liver adenomatosis (in
624 6.5% of the cases according to a study), a rare disease that can lead to severe
625 abdominal hemorrhage⁸³. Therefore, it is recommended to screen carriers in the
626 families for liver tumours, as preventive surgical or non-surgical procedures can be
627 discussed to prevent the risk of liver bleeding, especially when adenomas are
628 numerous or large⁸³.

629 **Dominant *KCNJ11*- or *ABCC8*-diabetes**

630 As mentioned above, pathogenic, activating, heterozygous mutations in the two ATP-
631 dependent potassium channel genes *KCNJ11* and *ABCC8*, which cause neonatal
632 diabetes, can also lead to MODY or even typical type 2 diabetes. Their treatment of
633 choice is relatively high dosage of sulfonylureas as SUR1 (encoded by *ABCC8*) is
634 the ligand of this class of drugs which generally enables long-term excellent glucose
635 control^{84,85}. However, if the transfer from insulin is successful for most patients with
636 dominant *KCNJ11*-diabetes, the good response to sulfonylurea is best predicted by
637 the *in vitro* response of the specific mutation and the duration of diabetes⁸⁶. This
638 result strongly supports the early genetic testing and early treatment change⁸⁶.

639 Neurological features, especially epilepsy, impaired cognition, motor function and
640 muscular tone, visuo-motor integration, and attention deficits are frequent in children
641 and adults carrying pathogenic mutations in *KCNJ11* or *ABCC8*⁸⁷. A recent meta-
642 review of 34 publications showed that the sulfonylurea glibenclamide significantly
643 improved neurological abnormalities in these patients, but earlier treatment initiation
644 was associated with greater benefits. Hypotonia was the symptom that responded
645 best⁸⁷.

646 **Other forms of monogenic diabetes**

647 There is no specific treatment for the other types of monogenic diabetes. These
648 patients are often treated with insulin injections⁸⁸. This is the case for dominant
649 *HNF1B*-diabetes. Unlike patients with dominant *HNF1A*- or *HNF4A*-diabetes, those
650 deficient for *HNF1B* do not respond adequately to treatment with sulfonylureas,
651 possibly due to comorbid pancreatic hypoplasia and some degree of hepatic insulin
652 resistance⁸⁹. However, the genetic diagnosis of monogenic diabetes should be
653 carefully followed in many cases by the monitoring of extra-pancreatic development
654 abnormalities: more commonly in heart in patients deficient for *GATA4* or *GATA6*,
655 and in the renal and genitourinary organs in patients deficient for *HNF1B*^{21,49,63}. It is
656 noteworthy that in many cases the impaired development of the heart found in
657 *GATAs* mutations has led to surgery at birth, a history that should be elicited while
658 evaluating early-onset diabetes in order to guide the genetic screening.

659 Specific lifestyle and dietary modifications are not different from common forms of
660 type 1 diabetes and type 2 diabetes with reasonable physical activity (avoiding
661 hypoglycemia) and a balanced diet avoiding high glycemic index food⁹⁰. Of note,
662 most patients with monogenic diabetes are not obese (Figure 3), and thus weight
663 loss is generally not an issue to be fixed by lifestyle modifications.

664 **Quality of life**

665 Monogenic diabetes is genetically and phenotypically heterogeneous and the clinical
666 care of its different subtypes is diversely demanding. However, the genetic diagnosis
667 of monogenic diabetes usually increases the quality of life of patients and their family
668 and decreases their anxiety about their future children^{91,92}. This is obvious for
669 dominant *GCK*-diabetes, as the prognosis of glucokinase deficiency is benign and,
670 thus, diagnosing this mild form of hyperglycemia is “good news”. However, the

671 condition should not be forgotten especially in women considering future
672 pregnancies. For dominant *HNF1A*- and *HNF4A*-diabetes, low dosage sulfonylureas
673 with or without GLP1 analogues has greatly improved the quality of life of these
674 patients⁷, and it is likely that it will be beneficial for the long-term health of these
675 patients. The situation is the same for patients dominant *KCNJ11*- or *ABCC8*-
676 diabetes. Indeed, in contrast to patients with common type 2 diabetes, there is no
677 long-term beta-cell desensitization to sulfonylureas and excellent glucose control
678 remains for decades⁸⁵. Unfortunately, for patients with one of the other forms of
679 monogenic diabetes, insulin therapy is generally required which is as challenging as
680 in patients with type 1 diabetes. With regard to long-term disability, the most worrying
681 situation concerns dominant *HNF1B*-diabetes as infertility and even end-stage renal
682 failure are possible⁶³. Close follow up of these patients is necessary.

683 Studies in 2011 and 2014 have evaluated the cost-effectiveness of neonatal diabetes
684 and MODY genetic testing, respectively^{91,92}. Main outcome measures were costs and
685 quality-adjusted life years (QALYs) based on lifetime risk of complications and
686 treatments, expressed as the incremental cost-effectiveness ratio (ICER). Genetic
687 diagnosis targeting *KCNJ11* and *ABCC8* was particularly cost-efficient with a good
688 0.32 QALYs at 10 years and 0.70 at 30 years, along with an ICER of \$200,000 per
689 QALY⁹². Testing *GCK*, *HNF1A* and *HNF4A* in patients between the ages of 25–40
690 years with presumed type 2 diabetes yielded an average gain of 0.012 QALY and
691 resulted in an ICER of \$205,000 per QALY, considering a MODY prevalence of 2%⁹².
692 An increase in MODY prevalence from 2 to 6% would lead to an ICER of about
693 \$50,000 per QALY, which is frequently used as the threshold for assessing cost-
694 effectiveness of a health intervention⁹¹. It is noteworthy that this study was based on
695 the expensive and labor-intensive Sanger sequencing (*i.e.* \$2,580 per individual
696 tested). The decrease in the cost of genetic testing (*e.g.* using next-generation
697 sequencing methodologies that are much more economical and quick to run) from
698 \$2,580 to \$700 led to an ICER of \$50,000 per QALY⁹¹. A more recent article has
699 confirmed that the widespread implementation of genetic diagnosis along with
700 screening of biomarkers (*i.e.* negativity for islet cell autoantibodies and positivity for
701 C-peptide) could improve the lives of patients with MODY while saving the health
702 system money (increased average quality of life [0.0081 QALY] and decreased costs
703 [-\$735] per patient)⁹³. Adding cascade genetic testing (*i.e.* testing first-degree

704 relatives of probands) further improved the lives of patients and substantially
705 decreased costs⁹³.

706 **Outlook**

707 Monogenic diabetes research has truly revolutionized our understanding of the
708 pathophysiology of diabetes and the genetics of common diseases⁶: it has been one
709 of the first proof of concepts that a very prevalent and complex disorder could be
710 caused by a single gene defect. Later on, further models of complex traits including
711 obesity but also heart diseases or Alzheimer disease have emerged, showing a
712 continuum between rare and common forms of diseases. As mentioned above,
713 depending of the nature of the DNA variant, the same monogenic diabetes genes
714 can contribute to different forms of diabetes with early or late onset. This spectrum of
715 diabetes phenotypes can also be observed for a single specific pathogenic mutation
716 shared by different carriers. Therefore, a boundary between monogenic diabetes and
717 type 2 diabetes is less obvious than the community thought 20 years ago. These new
718 findings have dramatic consequences on diabetes management: a non-negligible
719 part of patients with “typical” common forms of type 2 diabetes actually carry a
720 pathogenic mutation in a monogenic diabetes gene, and thus they may potentially be
721 treated differently than those who have common, truly polygenic type 2 diabetes⁵.

722 Monogenic diabetes research (along with genome-wide association studies related to
723 type 2 diabetes) has also radically modified our understanding of the pathophysiology
724 of non-autoimmune diabetes. Indeed, before 1992, when dominant *GCK*-diabetes
725 was discovered, insulin resistance was considered as the primary abnormality
726 eventually leading to abnormal glucose control with secondary exhaustion of
727 pancreatic insulin-secreting cells. Monogenic diabetes research has demonstrated
728 for the first time that inherited defects in insulin secretion can cause diabetes, even at
729 a young age, without the need for severe insulin resistance or concurring obesity. Far
730 later, genome-wide association studies (in combination with other genomic analyses
731 or *in vitro* assays) have also shown that (i) type 2 diabetes-associated single
732 nucleotide polymorphisms (SNPs) are enriched in regulatory regions that are active
733 in pancreatic islets and not in tissues related to insulin resistance^{94,95}; (ii)
734 susceptibility genes for common type 2 diabetes (*i.e.* close to type 2 diabetes-
735 associated SNPs) are involved in insulin secretion far more frequently than in insulin

736 resistance⁹⁶. In this respect, monogenic diabetes genes and susceptibility genes for
737 common type 2 diabetes are mostly involved in the development and function of
738 pancreatic beta cells.

739 If monogenic diabetes research in the past 30 years has been very successful,
740 several gaps remain to be filled. Several hypotheses could explain why the etiology
741 of hyperglycemia in some patients with atypical diabetes remain unclear even after
742 state-of-the-art attempt of genetic diagnosis:

743 (i) These patients may actually have a polygenic form of type 2 diabetes with very
744 early age of onset (*e.g.* due to the presence of type 2 diabetes in both paternal and
745 maternal lineages). Polygenic risk scores for type 2 diabetes derived from genome-
746 wide association studies should be systematically analyzed as these MODY-like
747 patients maybe in the upper range of the polygenic risk scores, which borders the
748 risk scores for diabetes of pathogenic mutations in monogenic diabetes genes⁹⁷.

749 (ii) Alternatively, these patients may carry a deleterious mutation in a non-coding
750 regulatory region of a monogenic diabetes gene. An elegant study showed that
751 deleterious homozygous non-coding mutations in a distal *PTF1A* enhancer led to
752 neonatal diabetes due to pancreatic agenesis⁹⁸. Therefore, whole-genome
753 sequencing (along with genomic analyses) would be the only way to elucidate these
754 cases.

755 (iii) Of course, it is possible that other, as yet unknown but very rare monogenic
756 diabetes genes remain to be identified.

757 That advocates for a graded approach in the diagnosis of monogenic diabetes
758 including, first, whole-exome sequencing with a focus on known monogenic diabetes
759 genes. If negative, the mutation analysis should be extended to candidate genes for
760 diabetes or should be included in a gene-centric analysis, including other
761 unelucidated cases and elderly normal glucose controls, in order to find new
762 monogenic diabetes genes. In parallel, whole-genome sequencing and DNA
763 microarray genotyping may be performed. The situation is quite different in non-
764 European ancestries (*e.g.* Asians, Africans) where only a minority of cases have
765 been elucidated, so far¹¹. A specific effort of screening these populations by all
766 possible means (*i.e.* whole-exome sequencing, whole-genome sequencing, DNA
767 microarrays) is needed to make further progress in these ethnicities.

768 Despite strong initial hopes with GCK activators⁹⁹, no drug directly derived from
769 monogenic diabetes research has been developed yet and introduced into the

770 market. GCK activators failed since their effect on insulin secretion was modest (with
771 diminished long-term efficacy) and they had adverse effects on the liver, with the
772 development of steatosis and hypertriglyceridemia directly linked to increased liver
773 glucokinase activity¹⁰⁰. To our knowledge, no other promising drug target directly
774 coming from monogenic diabetes research has emerged so far. Ironically, the first
775 ever anti-diabetic drug family, the sulfonylureas, which directly targets SUR1
776 encoded by *ABCC8*, has a much better long term efficacy in monogenic diabetes
777 than in patients with common type 2 diabetes⁴⁵. Of note, families where three
778 generations of patients with apparent type 2 diabetes are well controlled by
779 sulfonylureas may actually carry a mutation in *ABCC8*, *KCNJ11*, *HNF1A* or *HNF4A*⁵⁵.
780 Further efforts may provide new clues. This is very important since the majority of
781 patients with type 2 diabetes fail to achieve treatment objectives (in term of glucose
782 control, weight management etc.), and innovative molecules restoring normal insulin
783 secretion are lacking. More efforts directed to the pathways involving monogenic
784 diabetes genes in pancreatic beta cells may reveal novel drug targets.

785 The priorities for basic and clinical research and precision medicine centered on
786 monogenic diabetes may be summarized as follows: (i) developing economical, quick
787 and reliable gene screening methodologies and high throughput pipelines that can be
788 disseminated in every country to diagnose most of the patients with monogenic
789 diabetes whatever their age is and their phenotype looks like; (ii) making more
790 progress in developing specific treatments for monogenic diabetes gene mutation
791 carriers as their long-term health (especially in dominant *HNF1A*- or *HNF4A*-
792 diabetes) is still uncertain – an effort that implies having an efficient follow-up of
793 every patient diagnosed with monogenic diabetes; (iii) further advancing our
794 knowledge on pancreatic beta-cell biology by leveraging the outcomes of monogenic
795 diabetes research.

796

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811 **Conflict of Interest**

812 The authors declare no competing interests.

813

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1202 **highlighted the incomplete penetrance of pathogenic mutations in syndromic**
1203 **monogenic diabetes genes. Indeed, these mutations were found in patients**
1204 **with a suspicion of non-syndromic monogenic diabetes.**

1205 **Tables**

1206 **Table 1 | Identification and inheritance mode of monogenic diabetes**
 1207 **genes**

Gene	Inheritance mode	Location	Ref.
MODY (without other atypical features)			
<i>GCK</i>	AD/AR	7p13	2,3
<i>HNF1A</i>	AD	12q24.31	16
<i>HNF4A</i>	AD	20q13.12	17
<i>PDX1</i>	AD	13q12.2	101
<i>HNF1B</i>	AD	17q12	102
<i>NEUROD1</i>	AD	2q31.3	103
<i>CEL</i>	AD	9q34.13	18
<i>INS</i>	AD	11p15.5	37
<i>ABCC8</i>	AD	11p15.1	104
<i>KCNJ11</i>	AD	11p15.1	50
<i>GATA6</i>	AD	18q11.2	21
<i>WFS1</i>	AD/AR	4p16.1	105
<i>TRMT10A</i>	AR	4q23	106
<i>PCBD1</i>	AR	10q22.1	107
<i>GATA4</i>	AD	8p23.1	49
<i>APPL1</i>	AD	3p14.3	108
<i>RFX6</i>	AD	6q22.1	109
<i>MAFA</i>	AD	8q24.3	110
<i>SLC19A2</i>	AD/AR	1q24.2	30
<i>ONECUT1</i>	AD	15q21.3	111
<i>m.3243A>G</i>	maternally	Mitochondria	52
<i>KCNK16</i>	AD	6p21.2	27
Neonatal Diabetes (without other atypical features)			
<i>HNF1B</i>	AD	17q12	101
<i>GCK</i>	AR	7p13	36
<i>KCNJ11</i>	AD/AR	11p15.1	113
<i>ABCC8</i>	AD/AR	11p15.1	114
<i>INS</i>	AD/AR	11p15.5	115
<i>GATA6</i>	AD	18q11.2	116
<i>GATA4</i>	AD	8p23.1	49
Syndrome including Neonatal/Early-Onset Diabetes			
<i>m.3243A>G</i>	maternally	Mitochondria	117
<i>HNF1B</i>	AD	17q12	102
<i>AIRE*</i>	AR/AD	21q22.3	118,119
<i>PDX1</i>	AR	13q12.2	120
<i>SLC2A2</i>	AR	3q26.2	28
<i>WFS1</i>	AR/AD	4p16.1	121,122
<i>SLC19A2</i>	AR	1q24.2	29
<i>EIF2AK3</i>	AR	2p11.2	123
<i>FOXP3*</i>	XR	Xp11.23	124
<i>PTF1A</i>	AR	10p12.2	125
<i>GLIS3</i>	AR	9p24.2	126
<i>CEL</i>	AD	9q34.13	18
<i>PAX6</i>	AR	11p13	127
<i>STAT5B*</i>	AR	17q21.2	128
<i>CISD2</i>	AR	4q24	129
<i>RFX6</i>	AR	6q22.1	130
<i>NEUROD1</i>	AR	2q31.3	131
<i>NEUROG3</i>	AR	10q22.1	132
<i>IER3IP1</i>	AR	18q21.1	133
<i>ZFP57</i>	AR	6p22.1	134
<i>MNX1</i>	AR	7q36.3	135
<i>GATA6</i>	AD	18q11.2	21
<i>DNAJC3</i>	AR	13q32.1	136
<i>STAT3*</i>	AD	17q21.2	137
<i>TRMT10A</i>	AR	4q23	106

GATA4	AD	8p23.1	49
NKX2-2	AR	20p11.22	138
CDKN1C	AD	11p15.4	139
PPP1R15B	AR	1q32.1	140
LRBA*	AR	4q31.3	141
IL2RA*	AR	10p15.1	142
FOXA2	AD	20p11.21	143
CNOT1	AD	16q21	144
YIPF5	AR	5q31.3	145
EIF2B1	AD	12q24.31	146
MIA3	AR	1q41	147
STAT1*	AD	2q32.2	148
MANF	AR	3p21.2	149
ONECUT1	AR	15q21.3	111

- 1208 **AD**, autosomal dominant inheritance; **AR**, autosomal recessive inheritance; **XR**, X-
- 1209 linked recessive inheritance
- 1210 *Genes causing auto-immune diabetes
- 1211 Additional MODY genes have been described in *BLK*, *KLF11* and *PAX4* but the
- 1212 evidence in support of these gene-disease associations has been refuted⁷³.

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1214

Table 2. | Expression of monogenic diabetes genes and nature/location of encoded proteins

Gene	Protein type	Location	TPM adult beta cell	TPM fetal beta cell	TPM adult islet	Other hits
<i>ABCC8</i>	Channel subunit	Membrane	1010	232	226	Brain (cerebellum), pituitary
<i>KCNJ11</i>	Channel subunit	Membrane	34	28	11	Skeletal muscle, pancreas, brain (cerebellum), heart, thryroid, stomach, pituitary
<i>KCNK16</i>	Channel subunit	Membrane	182	97	68	None
<i>SLC2A2</i>	Transporter	Membrane	10	1	10	Liver, Small intestine
<i>SLC19A2</i>	Transporter	Membrane	9	9	11	Ubiquitous
<i>GCK</i>	Enzyme	Cytosol	30	68	25	Liver
<i>APPL1</i>	Protein binding	Cytosol	42	17	14	Ubiquitous
<i>CEL</i>	Enzyme	Cytosol	-	-	86	Pancreas
<i>CNOT1</i>	Protein/RNA binding	Cytosol	-	-	71	Ubiquitous
<i>LRBA*</i>	Protein binding	Cytosol	62	43	19	Ubiquitous
<i>INS</i>	Hormone	Granule	205700	83300	37000	None
<i>PAX6</i>	Transcription factor	Nucleus	261	333	122	Brain (cerebellum)
<i>PCBD1</i>	Enzyme	Nucleus	53	113	48	Ubiquitous
<i>RFX6</i>	Transcription factor	Nucleus	79	107	18	None
<i>PDX1</i>	Transcription factor	Nucleus	118	105	18	Pancreas
<i>CDKN1C</i>	Protein binding	Nucleus	107	27	54	Ubiquitous
<i>NKX2-2</i>	Transcription factor	Nucleus	104	42	16	Brain, pituitary
<i>NEUROD1</i>	Transcription factor	Nucleus	189	167	31	Brain (cerebellum)
<i>GLIS3</i>	Transcription factor	Nucleus	136	111	35	Thyroid
<i>STAT3*</i>	Transcription factor	Nucleus	110	32	81	Ubiquitous
<i>FOXA2</i>	Transcription factor	Nucleus	42	43	23	Liver, lung, stomach, pancreas, colon, thyroid
<i>NEUROG3</i>	Transcription factor	Nucleus	0	35	0	Brain (hippocampus), small intestine, colon
<i>MAFA</i>	Transcription factor	Nucleus	97	13	26	Skeletal muscle, testis
<i>STAT5B*</i>	Transcription factor	Nucleus	26	18	17	Ubiquitous
<i>STAT1*</i>	Transcription factor	Nucleus	43	10	68	Ubiquitous
<i>MNX1</i>	Transcription factor	Nucleus	35	21	9	Pancreas, colon, pituitary, stomach, small intestine
<i>HNF1B</i>	Transcription factor	Nucleus	5	23	16	Kidney, liver, lung, pancreas, bladder, colon, small intestine, stomach, testis
<i>HNF1A</i>	Transcription factor	Nucleus	10	22	5	Liver, kidney, pancreas, colon, small intestine, stomach
<i>HNF4A</i>	Transcription factor	Nucleus	5	12	15	Liver, kidney, pancreas, colon, small intestine, stomach
<i>GATA6</i>	Transcription factor	Nucleus	-	-	14	Ubiquitous
<i>GATA4</i>	Transcription factor	Nucleus	1	0	3	Pancreas, ovary, heart, testis, stomach, artery
<i>TRMT10A</i>	Enzyme	Nucleus	2	2	4	Ubiquitous
<i>ONECUT1</i>	Transcription factor	Nucleus	-	-	4	Liver, pancreas, testis
<i>FOXP3*</i>	Transcription factor	Nucleus	0	2	0	Blood, testis, spleen, skin, small intestine, lung, liver
<i>PTF1A</i>	Transcription factor	Nucleus	0	0	0	Pancreas
<i>ZFP57</i>	Transcription factor	Nucleus	0	0	0	Brain (spinal cord, substantia nigra)
<i>AIRE*</i>	Transcription factor	Nucleus	-	-	0	Brain
<i>IL2RA*</i>	Protein binding	Nucleus	0	0	1	Spleen, small intestine, lung
<i>WFS1</i>	Protein binding	ER	112	19	28	Ubiquitous
<i>MANF</i>	Protein/RNA binding	ER	93	46	86	Ubiquitous
<i>PPP1R15B</i>	Protein binding	ER	56	71	35	Ubiquitous
<i>IER3IP1</i>	Protein binding	ER	49	8	23	Ubiquitous
<i>EIF2B1</i>	Protein binding	ER	42	29	19	Ubiquitous
<i>MIA3</i>	Protein binding	ER	43	21	37	Ubiquitous
<i>DNAJC3</i>	Protein binding	ER	59	21	47	Ubiquitous
<i>YIPF5</i>	Protein transport	ER	-	-	41	Ubiquitous
<i>CISD2</i>	Protein binding	ER	15	8	28	Ubiquitous
<i>EIF2AK3</i>	Protein binding	ER	15	12	24	Ubiquitous

1215 *Genes causing auto-immune diabetes

1216 TPM in adult and fetal pancreatic beta cells are shown according to RNA-seq data published
1217 in ref¹⁵⁰. TPM in adult pancreatic islets are shown according to RNA-seq data published in
1218 ref¹⁵¹.
1219 **ER**, endoplasmic reticulum; **TPM**, transcript per million

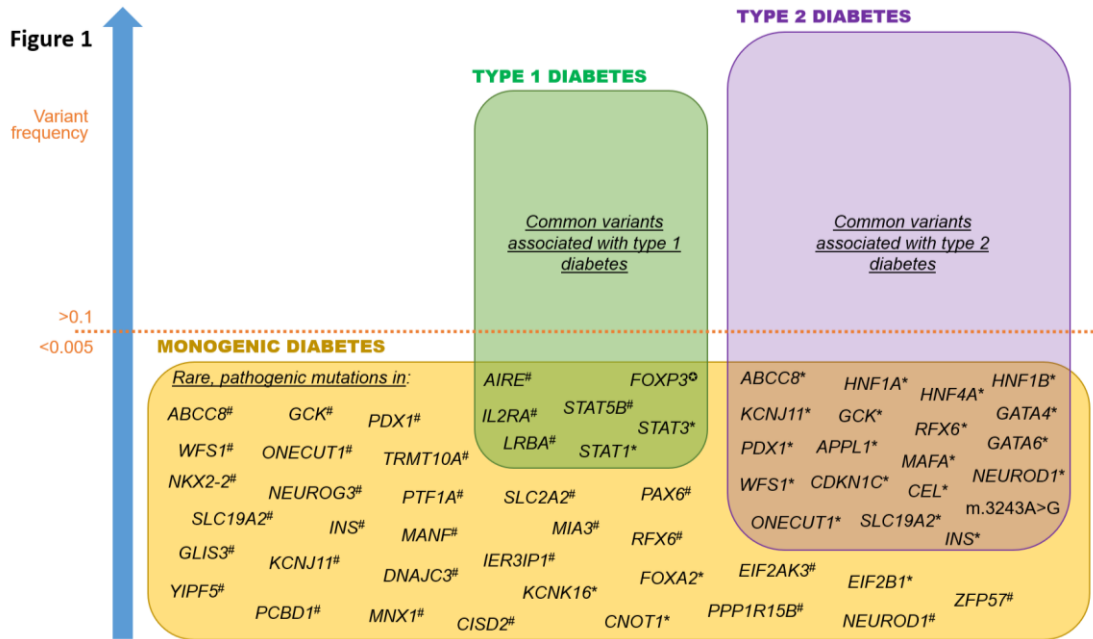
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1222 **Figure 1 | Overlapping between monogenic diabetes, type 1 diabetes and**
 1223 **type 2 diabetes**

1224 Genes harbouring rare pathogenic mutations leading to monogenic diabetes, type 1
 1225 diabetes and/or type 2 diabetes. #autosomal recessive inheritance; *autosomal
 1226 dominant inheritance; ♂X-linked recessive inheritance

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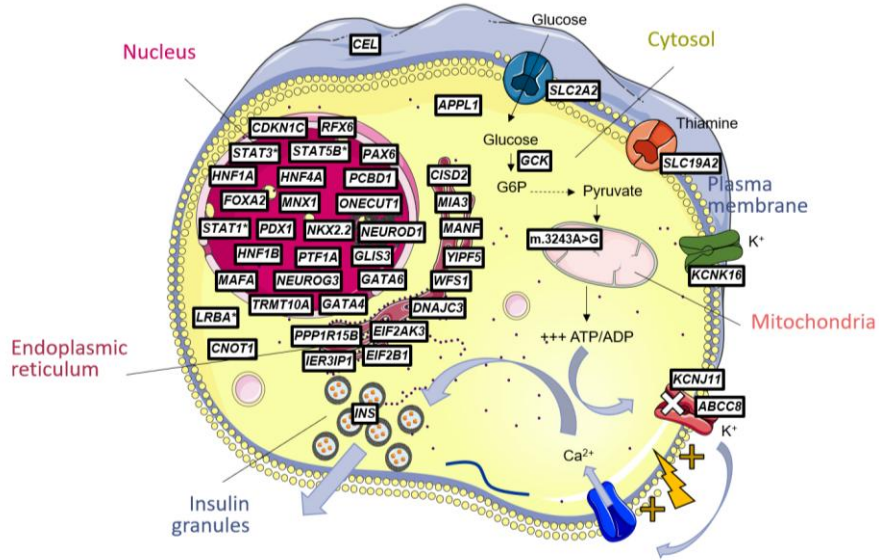


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1230 **Figure 2. | Monogenic diabetes genes in pancreatic beta cells**
 1231 Monogenic diabetes genes impact all compartments of pancreatic beta cells
 1232 including nucleus, endoplasmic reticulum, plasma membrane, mitochondria etc.
 1233 *Genes linked with auto-immune diabetes. Only genes that are expressed in human
 1234 islets or beta cells are shown in this figure

Figure 2



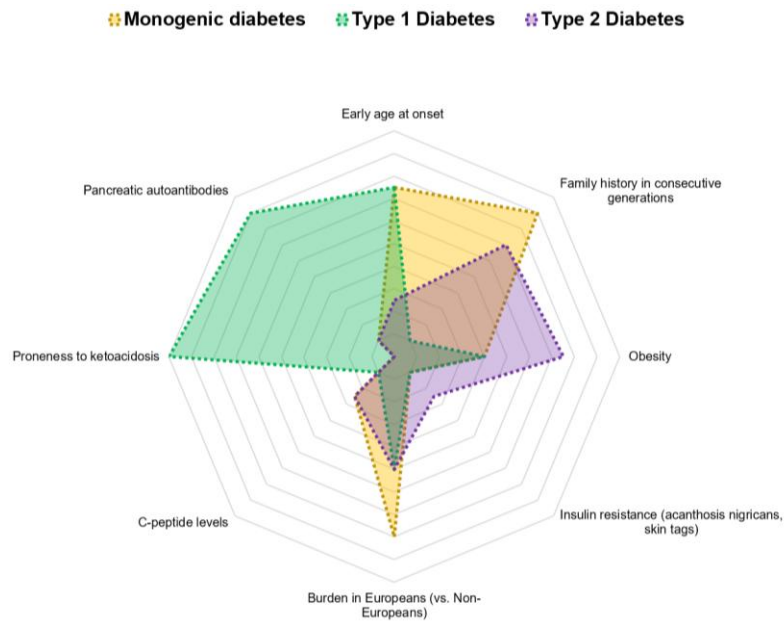
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1237 **Figure 3 | Differentiation between monogenic diabetes, type 1 diabetes**
1238 **and type 2 diabetes, based on clinical presentation and ancestry**

1239 Clinical presentation features that differentiate monogenic diabetes, type 1 diabetes
1240 and type 2 diabetes at the time of diagnostic. Ideas of magnitude have been shown
1241 in this flow chart based on multiple articles in the literature^{5,9,11,152,153} and on the
1242 definition of type 1 diabetes, type 2 diabetes and monogenic diabetes.

Figure 3



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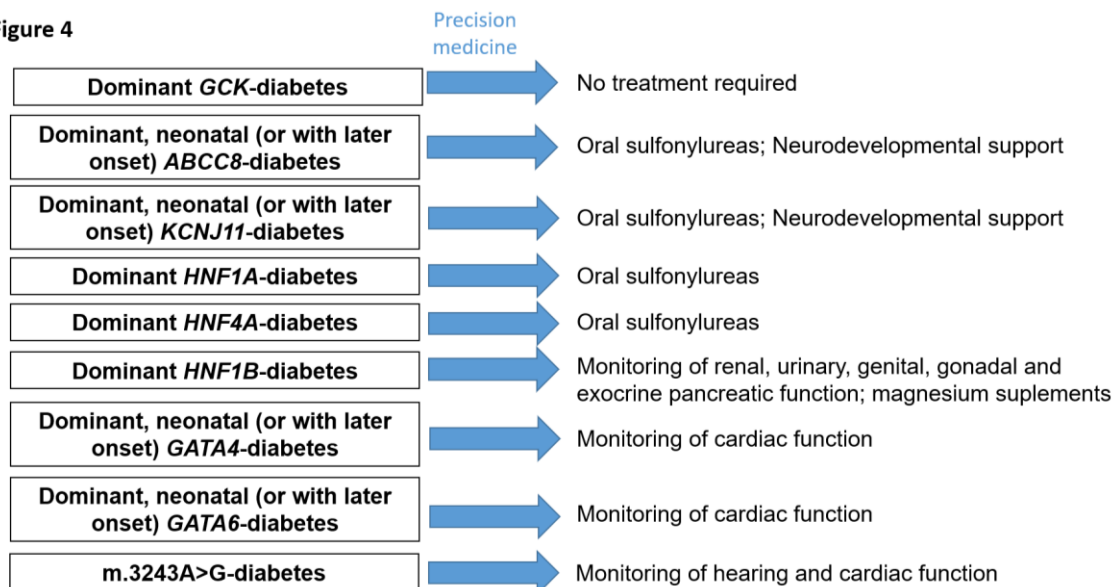
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Figure 4 | Actionable genes linked with monogenic diabetes

Precision medicine can be applied in several monogenic forms of diabetes.

Figure 4



1247

1248 **Boxes**

1249

1250 **Box 1 | Monogenic diabetes-associated genes and technology used for**
1251 **their discovery**

1252

- 1253 • **Linkage analyses followed by Sanger sequencing of candidate genes in**
1254 **diabetes-associated linkage genomic peaks**

1255 *GCK, HNF1A, HNF4A, CEL, INS, WFS1, SLC19A2, CISD2, IER3IP1*

- 1256 • **Candidate gene strategy**

1257 *PDX1, HNF1B, NEUROD1, KCNJ11, ABCC8, GATA4, NEUROG3, AIRE,*
1258 *SLC2A2, PAX6, STAT5B, ZFP57*

- 1259 • **Homozygosity mapping followed by Sanger sequencing of candidate**
1260 **genes in runs of homozygosity (ROH)**

1261 *EIF3AK3, FOXP3, PTF1A, GLIS3*

- 1262 • **Candidate variant strategy**

1263 *m.3243A>G*

- 1264 • **Next-generation sequencing**

1265 *GATA6, MNX1, DNAJC3, STAT3, APPL1, MAFA, KCNK16, PPP1R15B,*
1266 *LRBA, IL2RA, FOXA2, CNOT1, YIPF5, EIF2B1, MIA3, STAT1, MANF*

- 1267 • **Linkage analyses and next-generation sequencing**

1268 *TRMT10A, PCBD1, CDKN1C*

- 1269 • **Homozygosity mapping and next-generation sequencing**

1270 *RFX6, NKX2-2, ONECUT1*