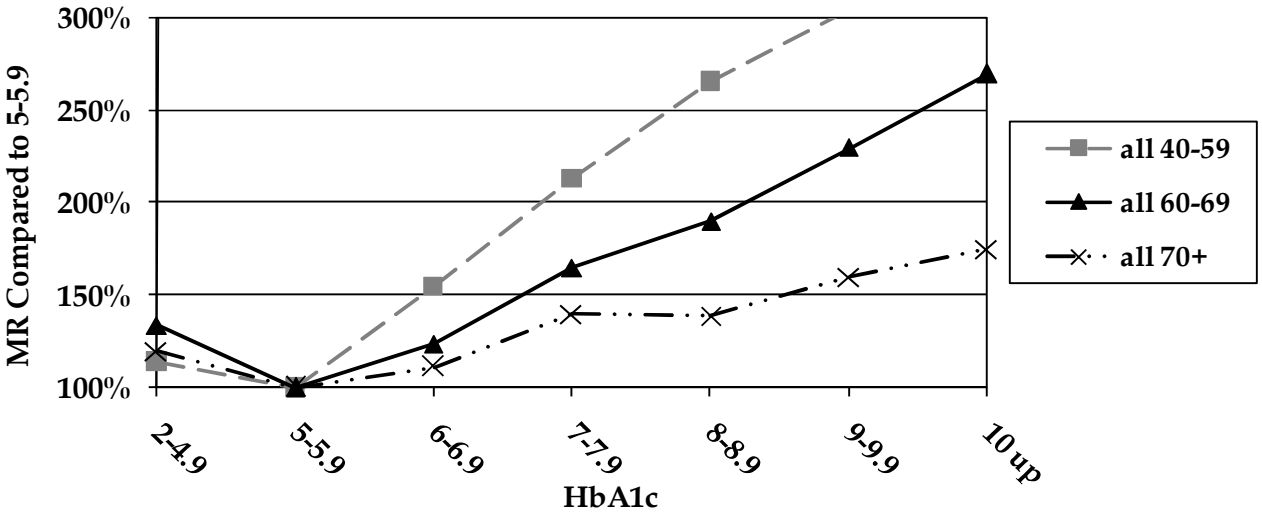
Optimizing Fructosamine and HbA1c to reduce mortality and cost

Objective: To identify optimal usage of fructosamine as a screen and HbA1c as a measure of chronically elevated serum glucose to predict mortality risk. This is CRL proprietary information for internal use at your company only.

Background: This is an update of the 2008 CRL bulletin. The section on mortality associated with HbA1c elevations (based on work published in the J Insur Med) is expanded slightly but otherwise unchanged. However, in 2009, the reagent used for the fructosamine test was changed and as of 11-09, the fructosamine standardization was readjusted as well. This, along with more underwriting attention being paid to HbA1c values of 6-6.9%, called for a fresh review.

Approximately 5% of applicants ages 20-39 now have a HbA1c of 6.1% or higher and for those age 40+, that is now 20%. With the increasing prevalence of chronically elevated blood sugars associated with increasing obesity and the emphasis on competitive preferred categories, effective screening for HbA1c elevations is critical to control mortality.

Facts: Two studies were conducted. **The first study** (published articles available at www.crlcorp.com/insurance/stayinformed.htm) involved using the Social Security Death Master File to follow mortality in 286,000 applicants age 40 and over tested for HbA1c by companies, typically on a reflex basis. Results follow:



Values in the 5-5.9% range had the lowest mortality. In contrast to some smaller clinical studies, there was no difference in mortality between the 5-5.4% and 5.5-5.9% groups. The number of deaths in this band was 5 to 10 times the number from Khaw (Annals of Internal Medicine 2004) which found a difference but had widely overlapping confidence intervals.

Values 6% and higher had increased mortality which was linear and varied by age. Though raw mortality varied by sex, the mortality ratios were identical so data from both sexes was combined. Likewise the mortality pattern and ratios for ages 40-49 and 50-59 were similar so they were combined into one band. Mortality remained linear even at higher HbA1c values.

Most HbA1c tests were performed based on elevated fructosamine so HbA1c values under 5% were few in number but had increased mortality. These probably represented situations where the screening result was elevated but HbA1c low and likely indicated high red cell turnover or abnormal hemoglobin.

Using these results, the following table of approximate excess risk can be constructed.

Table 1

Excess Relative Risk (%) by Age

HbA1c %	**40-59**	**60-69**	**70+**
<5	>0	>0	>0
5-5.9	0	0	0
6-6.9	50	25	10
7-7.9	100	75	50
8-8.9	150	100	50
9-10.9	200	150	75
11+	300	175	100

Excess relative risk = (MR – 100%) with 100% taken from reference band of HbA1c 5 to 5.9%.

Risk increases with age and with level of HbA1c across the entire spectrum of values from 6% up. For example, the risk for HbA1c of 6-6.9% for ages 40-59 is listed as 150% of that for a HbA1c <6%. It could be estimated that that risk level might be 125% for HbA1c of 6-6.4% and 175% for HbA1c of 6.5-6.9%. Risk for all elevations is obviously higher at ages <40.

The second CRL study evaluated the sensitivity and specificity of the current fructosamine test in picking up elevated HbA1c values. This study was performed during November, 2009, on samples from clients where HbA1c testing was universal for ages 20+. Results may vary for other laboratories since (unlike HbA1c) standardization varies.

While Table 2 isolates the impact of fructosamine screening and blood sugar screening, it is Table 3 that approximates the combined percentage of HbA1c elevations likely found in the real world. A few additional applicants with HbA1c above 7% would likely also be found by history.

Table 2 Sensitivity of fructosamine or BS by HbA1c levels for all ages

% of elev. HbA1c found at various reflex cut-offs of fructosamine (mmol/L) or by use of BS reflex at 110 or 125 mg/dL (for all ages)

HbA1c	% found by fructosamine cut-off of:					% by BS of:	
% range	2.1+	1.9+	1.8+	1.7+	1.6+	110+	125+
6	<1%	6%	9%	31%	58%	7%	2%
6.1-6.4	1%	8%	18%	38%	63%	16%	6%
6.5-6.9	5%	24%	37%	58%	80%	44%	26%
7-7.9	24%	60%	74%	91%	96%	63%	44%
8+	82%	94%	97%	99%	99%	81%	75%

Table 3 Total estimated % of elevated HbA1c captured by BS 110+ and by fructosamine elevation combined

HbA1c	2.1+	1.9+	1.8+	1.7+	1.6+
% range	BS 110	BS 110	BS 110	BS 110	BS 110
6	7%	13%	15%	35%	60%
6.1-6.4	17%	23%	32%	47%	70%
6.5-6.9	46%	57%	66%	75%	88%
7-7.9	72%	90%	92%	96%	99%
8+	97%	97%	99%	100%	100%

From Table 3 we can see how large a percentage of HbA1c elevations will be captured using a combination of a particular fructosamine reflex cut-off (mmol/L) and a blood sugar cut-off of 110+ mg/dL. Tighter blood sugar cut-offs of 105 and 100 mg/dL were also explored. At HbA1c values from 6.1 to 6.4%, 100 mg/dL captured an additional 12% of HbA1c elevations in absence of fructosamine. In combination with fructosamine, the additional percentage captured is reduced to approximately 6%. That gain is reduced at higher HbA1c values.

Next we need to know, using any combination, how many HbA1c tests are generated since that controls the testing cost. That number (expressed as a % of all samples) is calculated in the following tables by adding together the number of true positives (based on age band prevalence) captured by screening plus the number of false positives generated. Table 4 lists the impact of fructosamine and blood sugar separately. Table 5 estimates the combined (real-world) impact.

Table 4 Estimated % of samples reflexed to HbA1c based on fruct reflex cut-off or BS cut-off

Based on prevalence of HbA1c elevation in applicants of 5% age <40 and 20% age 40+.

	% false pos. (HbA1c <6) for each fructosamine cut-off					% false pos. for BS	
	2.1+	1.9+	1.8+	1.7+	1.6+	BS 110+	BS 125+
Age 20-39	<1%	2%	8%	25%	50%	2%	1%
Age 40+	<1%	3%	10%	27%	53%	3%	1%

Table 5 Total estimated % of all samples reflexed to HbA1c based on fructosamine cut-off shown and BS 110+

	2.1+ BS 110	1.9+ BS 110	1.8+ BS 110	1.7+ BS 110	1.6+ BS 110
Age 20-39	4%	6%	12%	29%	56%
Age 40+	8%	12%	23%	43%	65%

The results from Table 5 should be similar to what you will see using each of the fructosamine reflex cut-offs with a blood sugar cut-off of 110+. More HbA1c tests are generated for ages 40+ because the average blood sugar is higher, resulting in more true and false screening positives. Companies have different age mixes and levels of obesity in applicants, so there will be some variation for each client company. Using a blood sugar cut-off of 100 rather than 110 mg/dL roughly triples the number of sample reflexed based on blood sugar.

Use the results of **Table 3** in combination with **Table 5** to compare the number of elevations missed vs. cost based on number of HbA1c tests generated. A fructosamine reflex cut-off of 1.6 mmol/L is the lower limit of practicality. If this still results in too many missed HbA1c elevations, then universal testing with HbA1c from age 20, 30 or 40 up is another alternative.

Discussion: HbA1c is the best single measure of chronic blood sugar elevation and mortality risk associated with that elevation. A level of 6.5% has now been proposed by the International Expert Committee as a diagnostic criteria for diabetes with a level of 6.0% indicating higher risk.

The HbA1c test, however, costs several dollars so cheaper screening tools are desirable and a combination of fructosamine and blood sugar is often used. Recognition of the risk associated with even small elevations of HbA1c, combined with increased levels of obesity and the emphasis on preferred categories, make test sensitivity an ever more important consideration. Clearly, fructosamine has limitations in finding HbA1c values <7% even at a cut-off of 1.6 mmol/L where 60% of applicants will likely be reflexed to HbA1c. Lowering the blood sugar cut-off from 110 to 100 mg/dL appears less efficient than lowering the fructosamine cut-off.

Cost-benefit analysis (data not shown) suggests a substantial net benefit for universal HbA1c testing from age 40+ if underwriting action is planned down to HbA1c values of 6 or 6.1%. Even below age 40, benefit easily covers cost. If testing cost is critical, fructosamine in conjunction with blood sugar, etc. may be a reasonable alternative but a cut-off value below 2.1 will be needed if finding HbA1c values below 7 is important.

Conclusions:

- The HbA1c level, not a diagnostic label, is the prime component in establishing mortality risk.
- Mortality increases from a HbA1c of 6% up in a linear fashion with a steeper increase at younger ages.
- In insurance applicants, there is no evidence of a mortality difference between 5 to 5.9%.

- Higher fructosamine reflex levels such as 2.1 mmol/L with blood sugar reflex at 110 mg/dL generate only a few false positive HbA1c results but are relatively ineffective at picking up HbA1c values below 7% and miss some between 7 to 7.9%.
- Finding the majority of those values 6-6.9% requires a fructosamine cut-off of 1.6+ which, in combination with a BS reflex of 110+, reflexes to HbA1c for approximately 60% of samples (averaged across all ages).
- Finding the remaining 30% of those with HbA1c values 6.1-6.4 and capturing all those 7-7.9% (if not identified as diabetic) requires use HbA1c for all samples.

- Using a reflex level for blood sugar of 110+ adds needed sensitivity for higher fructosamine reflex cut-off values with few false positives and is still useful even with lower fructosamine reflex cut-off values since cost and false positives are so low. Dropping this level to 100 or 105 mg/dL is less efficient than lowering the fructosamine cut-off.