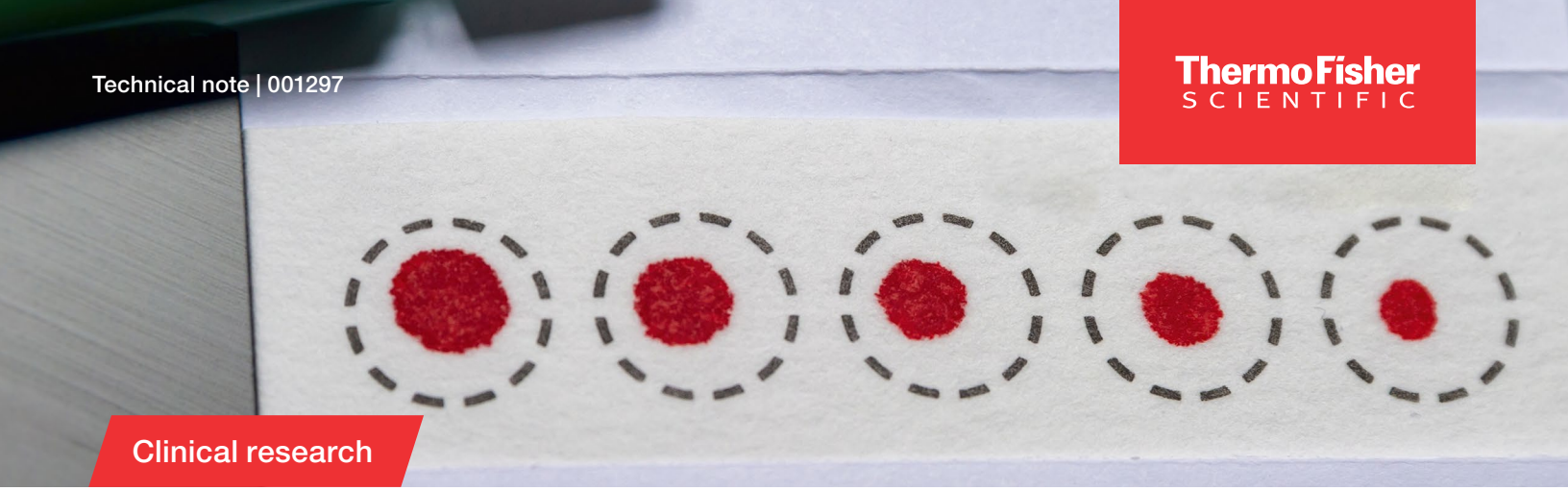
Technical note | 001297



Clinical research

A reliable and simple FIA-MS/MS method for the quantitation of amino acids, acylcarnitines, succinylacetone, and argininosuccinic acid in dried blood spots

Authors

Jingshu Guo, Richard J. Gibson, Stephanie Samra

Thermo Fisher Scientific, San Jose, CA, USA

Keywords

Vanquish MD HPLC, TSQ Quantis MD MS, TraceFinder LDT software, screening of newborns, inborn errors of metabolism, NeoMass AAAC Plus kit, dried blood spots, amino acid and acylcarnitine, succinylacetone, argininosuccinic acid, flow injection analysis-tandem MS

Goal

Develop and verify a semi-quantitation method to measure 15 amino acids, 13 acylcarnitines, succinylacetone, and argininosuccinic acid in dried blood spots via flow injection analysis-tandem MS (FIA-MS/MS) to meet the need for primary screening of the metabolic disorders in newborns

Introduction

The screening of newborns refers to various genetic and biochemical tests that occur within a few days of a newborn's life. Timely and properly conducted tests for newborns can lead to early diagnosis and treatment for genetic disorders and avoid severe health outcomes. In the U.S., state public health programs are encouraged to screen for inherited disorders specified in the Recommended Uniform Screening Panel (RUSP) from the U.S. Department of Health and Human Services (HHS), which includes 60 core and secondary disorders (as of July 2018).[1] From 2015 to 2017, the overall prevalence of congenital disorders was 34 per 10,000 newborns, and approximately 12,900 infants are expected to be identified with one of the disorders each year.[2]

Among the 60 disorders recommended for screening, 34 are readily detected by tandem-MS.[3] Measuring amino acids and acylcarnitines by mostly flow injection analysis-tandem MS (FIA-MS/MS) has been widely adopted as the methodology of the primary screening of metabolic disorders in programs for the screening of newborns. The abnormal levels of some amino acids and acylcarnitines are indicative of metabolic disorders in organic acid, fatty acid oxidation, and amino acid disorders. Recently, succinylacetone and argininosuccinic acid have been added to the list for the screening of newborns to identify Tyrosinemia type 1 and Argininosuccinic acidemia, respectively, as more appropriate biomarkers.[3]

In this report, an FIA-MS/MS method was developed on a Thermo Scientific™ Vanquish™ MD HPLC and a Thermo Scientific™ TSQ Quantis™ MD mass spectrometer (MS) equipped with heated electrospray ionization (HESI) in the selected reaction monitoring (SRM) mode. Quality control dried blood spot samples, reagents, and consumables were obtained from the NeoMass AAAC Plus kit (Ref 7100110, Labsystems Diagnostics Oy, Finland). The developed method verified the detection of 15 amino acids, 13 acylcarnitines, succinylacetone, and argininosuccinic acid from dried blood spot (DBS) samples, meeting the need for routine primary screening for inherited metabolic disorders in the state-sponsored program for the screening of newborns.

Experimental

Sample preparation

All chemicals and reagents were included in the NeoMass AAAC Plus kit (Ref 7100110, Labsystems Diagnostics Oy, Finland). Following the instructions, the lyophilized internal standards were first reconstituted using the extraction solution A (for acylcarnitine mix and succinylacetone) and extraction solution B (amino acid mix and argininosuccinic acid). A working solution was then prepared by combining the four IS solutions and diluting them 100-fold with Extraction Solution B. The control DBS cards have three levels (Levels I, II, and III). A 3.2 mm disc was punched from the DBS control cards and placed in the provided U-shaped 96 well plate. To start the analyte extraction, 25 µL of Extraction Solution A was added to soak the punched disc in the well for 5 min. A 90 µL aliquot of the IS working solution was then added to each well, which was sealed by the extraction cover and incubated for 30 minutes at 45 °C at 650 rpm. After the incubation, the well plate was left at room temperature to rest for 30 minutes. The entire extract from each well can be transferred to the provided V-shaped well plate, which was sealed by the analysis cover for the LC-MS analysis. Due to the limited stability of some IS, the unused IS solution was stored at -20 °C for up to one month, and the working solution was prepared immediately before use. The control DBS cards and the provided reagent were stored at 4 °C in an air-tight bag with desiccators. For the inter-day and intra-day precision measurement, each control level was prepared eight times over three days.

Liquid chromatography

A Vanquish MD HPLC was used to deliver the extracted analyte to MS via isocratic flow injection analysis. The LC-MS system was conditioned with at least 10 mL of the provided mobile phase prior to sample injection. Each sample was injected twice with an injection volume of 10 µL. The LC-MS/MS analysis was performed with an isocratic flow (100% provided mobile phase) at 0.15 mL/min for 1 minute.

Mass spectrometry

The analyte quantification was achieved using a TSQ Quantis MD mass spectrometer equipped with a Thermo Scientific™ OptaMax™ NG ion source with a HESI probe in both positive and negative modes. The MS source parameters and SRM properties are listed in Table 1. SRM transitions, optimized collision energies, RF lens settings, and dwell times for the compounds are shown in Table 2.

Data analysis

Data were acquired and processed using Thermo Scientific™ TraceFinder™ LDT software (ver 1.0). The analyte (A) concentrations were estimated based on the corresponding isotopically labeled internal standard (IS) using the equation:
Conc (A) = Area (A)/Area (IS) × Conc (IS)

Table 1. TSQ Quantis MD MS settings

MS Source Parameters	
Ion source type	HESI (OptaMax NG ion source)
HESI probe position	Center - 1.0 - L/M (x - y - z)
Spray voltage	+3,200 V; -2,800 V
Sheath gas (Arb)	50
Aux gas (Arb)	5
Sweep gas (Arb)	0
Ion transfer tube temp (°C)	325
Vaporizer temp (°C)	100
Ion source type	
Q1 Resolution (FWHM)	0.7
Q3 Resolution (FWHM)	1.2
CID Gas (mTorr)	1.5
Source Fragmentation	5

Table 2. SRM transitions, collision energies, and RF lens for the analytes and their internal standards

Positive ESI mode								
Analytes	Precursor (*m/z*)	Product (*m/z*)	IS	Precursor (*m/z*)	Product (*m/z*)	CE (V)	RF lens (V)	Dwell time (ms)
Alanine (Ala)	90.1	44.2	$^{2}H_4$-Ala	94.1	48.2	13	76	10
Arginine (Arg)	175.1	70.1	$^{2}H_4$,$^{13}C_6$-Arg	180.1	75.1	25	112	10
Aspartate (Asp)	134.1	74.0	$^{2}H_3$-Asp	137.1	75.0	17	75	10
Citrulline (Cit)	176.1	70.1	$^{2}H_2$-Cit	178.1	72.1	25	78	10
Glutamate (Glu)	148.1	84.1	$^{2}H_3$-Glu	151.1	87.1	18	77	10
Glycine (Gly)	76.1	30.1	^{13}C,^{15}N-Gly	78.1	32.2	13	51	10
Leucine (Leu)	132.1	86.1	$^{2}H_3$-Leu	135.1	89.1	11	72	10
Lysine (Lys)	147.1	84.1	$^{13}C6$,$^{15}N_2$-Lys	155.1	90.1	18	76	10
Methionine (Met)	150.2	61.2	$^{2}H_3$-Met	153.2	64.2	24	77	10
Ornithine (Orn)	133.2	70.2	$^{2}H_6$-Orn	139.2	76.2	19	65	10
Phenylalanine (Phe)	166.1	120.1	$^{13}C_6$-Phe	172.1	126.1	14	84	10
Proline (Pro)	116.2	70.2	$^{2}H_5$-Pro	121.1	74.2	16	78	10
Serine (Ser)	106.1	60.1	$^{13}C_3$-Ser	109.1	62.1	13	98	10
Tyrosine (Tyr)	182.1	91.1	$^{13}C_6$-Tyr	188.1	97.1	29	87	10
Valine (Val)	118.1	72.2	$^{2}H_8$-Val	126.1	80.2	13	97	10
Carnitine (C0)	162.1	85.0	$^{2}H_9$-C0	171.1	85.0	22	119	10
Acetylcarnitine (C2)	204.1	85.0	$^{2}H_3$-C2	207.1	85.0	21	116	10
Propionylcarnitine (C3)	218.1	85.0	$^{2}H_3$-C3	221.1	85.0	21	125	10
Butyrylcarnintine (C4)	232.2	85.0	$^{2}H_3$-C4	235.2	85.0	21	125	10
Isovalerylcarnitine (C5)	246.2	85.0	$^{2}H_9$-C5	255.2	85.0	23	137	10
Glutarylcarnitine (C5DC)	276.2	85.0	$^{2}H_3$-C5DC	279.2	85.0	25	129	10
Hexanoylcarnitine (C6)	260.2	85.0	$^{2}H_3$-C6	263.2	85.0	23	141	10
Octanoylcarnitine (C8)	288.2	85.0	$^{2}H_3$-C8	291.2	85.0	24	156	10
Decanoylcarnitine (C10)	316.2	85.0	$^{2}H_3$-C10	319.2	85.0	25	168	10
Dodecanoylcarnitine (C12)	344.2	85.0	$^{2}H_3$-C12	347.2	85.0	26	181	10
Tetradecanoylcarnitine (C14)	372.2	85.0	^{2}H9-C14	381.2	85.0	26	206	10
Hexadecanoylcarnitine (C16)	400.3	85.0	$^{2}H_3$-C16	403.3	85.0	28	213	10
Octadecanoylcarnitine (C18)	428.3	85.0	$^{2}H_3$-C18	431.3	85.0	29	233	10
Argininosuccinic acid (ASA)	291.0	70.2	$^{13}C_6$,$^{15}N_4$-ASA	300.9	75.2	31	134	10
Negative ESI mode								
Succinylacetone (SUAC)	157.2	99.0	$^{13}C_5$-SUAC	162.0	101.0	8	76	30

Results and discussion

Flow injection analysis-tandem MS (FIA-MS/MS) is the most commonly used primary screening method for the 33 metabolic disorders recommended by RUSP. In this technical note, we verified the detection of 15 amino acids, 13 acylcarnitines, succinylacetone, and argininosuccinic acid in DBS cards using the NeoMass AAAC Plus Kits. The quantification was achieved on the Vanquish MD HPLC and TSQ Quantis MD MS via SRM transition area ratio with the corresponding internal standards. The accuracy results and inter- and intra-day precision measurements of the three control DBS samples are specified in Tables 3a to 3c.

The examples of TraceFinder LDT software processing results using Ser (positive modes) and SUAC (negative mode) are shown in Figures 1a and 1b. The measured amounts, their %RSD, and %CV (of the peak area), are shown in the Sample Results table window. TraceFinder LDT software uses the caution flags to expedite the data review process. Samples outside the predefined acceptance criteria are flagged. The analyte and IS chromatograms from one raw file are shown in the Compound Details Plot, and the chromatograms of the same analyte, Ser and SUAC respectively, from different raw files are shown in Compound-Centric Plot.

Most of the measured values were within the specifications provided by the NeoMass AAAC Plus Control Value Ranges (µM), whereas the levels of some compounds, i.e., Ala, Arg, Cit, Val, and SUAC, were slightly lower. The target ranges were obtained from mass spectrometers other than those manufactured by Thermo Fisher Scientific, which may differ slightly on the ionization efficiency for the same compound. After consulting with Labsystems, it was concluded that the measured analyte levels were acceptable because the %RSD of all measured values were below 12%, indicating the method was robust and reproducible.

Table 3a. Inter-day and intra-day precision (Level I)

Analytes	Control values	Day-1		Day-2		Day-3		Inter-day	
	µM	Conc. (µM)	%CV	Conc. (µM)	%CV	Conc. (µM)	%CV	Conc. (µM)	%CV
Ala	222.22 (133.33-311.11)	112.47*	9.27	100.79*	8.11	109.46*	11.80	107.57*	5.64
Arg	17.79 (10.67-24.91)	9.43*	6.26	9.29*	7.75	9.39*	4.76	9.37*	0.77
Asp	244.38 (146.63-342.13)	173.66	9.24	185.17	8.46	179.25	7.00	179.36	3.21
Cit	33.78 (20.27-47.29)	25.85	6.75	23.64	9.10	27.06	4.96	25.52	6.80
Glu	254.88 (152.93-356.84)	232.57	5.26	225.17	9.46	228.82	5.72	228.86	1.62
Gly	273.23 (163.94-382.52)	224.05	7.46	224.31	10.43	219.84	8.18	222.73	1.13
Leu	106.46 (63.88-149.05)	89.19	5.78	90.93	7.99	89.26	3.91	89.79	1.09
Lys	95.88 (57.53-134.23)	91.06	6.18	93.26	7.17	88.46	4.72	90.93	2.64
Met	14.29 (8.57-20)	20.01	6.56	19.60	8.60	19.31	5.48	19.64	1.79
Orn	71.85 (43.11-100.59)	67.40	7.99	67.84	8.48	64.51	5.25	66.58	2.71
Phe	42.62 (25.57-59.67)	37.71	6.89	38.02	7.42	37.18	3.35	37.64	1.12
Pro	121.55 (72.93-170.17)	105.35	6.52	102.19	8.21	99.52	3.39	102.35	2.86
Ser	163.13 (97.88-228.38)	129.90	9.28	126.97	10.74	122.02	10.32	126.30	3.15
Tyr	57.28 (34.37-80.19)	61.75	6.50	62.17	6.71	61.16	4.53	61.70	0.82
Val	86.99 (52.2-121.79)	45.90*	8.45	47.95*	7.93	45.71*	4.52	46.52*	2.66
C0	17.18 (10.31-24.06)	13.51	7.58	13.83	6.83	13.00	6.02	13.45	3.08
C2	13.05 (7.83-18.27)	10.24	6.65	10.56	8.66	10.04	4.30	10.28	2.56
C3	2.32 (1.39-3.24)	1.87	6.00	1.94	8.80	1.83	4.98	1.88	3.09
C4	0.20 (0.12-0.28)	0.16	7.88	0.16	10.19	0.15	7.22	0.16	2.54
C5	0.22 (0.13-0.31)	0.17	9.02	0.17	8.11	0.16	5.98	0.17	2.90
C5DC	0.70 (0.42-0.99)	0.61	7.40	0.60	10.34	0.58	8.66	0.60	2.92
C6	0.09 (0.06-0.13)	0.08	9.67	0.08	9.85	0.08	6.88	0.08	3.80
C8	0.14 (0.09-0.2)	0.10	7.97	0.10	9.38	0.09	7.13	0.10	5.33
C10	0.04 (0.03-0.06)	0.03	13.10	0.03	10.72	0.03	9.06	0.03	9.15
C12	0.10 (0.06-0.14)	0.07	8.26	0.07	10.55	0.07	9.61	0.07	5.26
C14	0.12 (0.07-0.16)	0.11	7.06	0.11	11.22	0.10	5.93	0.11	3.90
C16	2.42 (1.45-3.38)	1.88	8.00	1.99	8.98	1.81	5.89	1.89	4.61
C18	0.92 (0.55-1.28)	0.71	8.54	0.80	9.96	0.72	4.65	0.74	6.70
ASA	18.80 (11.28-26.32)	13.59	5.66	13.13	9.54	13.06	9.56	13.26	2.19
SUAC	5.66 (3.39-7.92)	3.30*	8.32	3.56	10.33	3.52	9.22	3.46	3.99

* The measured levels were slightly lower than the target range, but this was determined to be acceptable (see the text for explanations).

Table 3b. Inter-day and intra-day precision (Level II)

Analytes	Control values	Day-1		Day-2		Day-3		Inter-day	
	µM	Conc. (µM)	%CV	Conc. (µM)	%CV	Conc. (µM)	%CV	Conc. (µM)	%CV
Ala	744.95 (521.46-968.43)	517.26*	6.39	490.86*	7.81	484.62*	6.73	497.58*	3.48
Arg	64.46 (45.12-83.8)	35.99*	3.02	34.73*	4.21	34.82*	3.52	35.18*	2.00
Asp	419.70 (293.79-545.61)	348.00	5.41	338.12	9.41	351.51	6.98	345.88	2.01
Cit	82.55 (57.78-107.31)	66.95	5.38	58.34	4.73	67.25	4.53	64.18	7.88
Glu	918.23 (642.76-1193.69)	860.88	4.38	837.45	3.36	804.73	4.92	834.35	3.38
Gly	852.88 (597.02-1108.74)	755.67	4.75	719.01	7.13	729.75	7.56	734.81	2.56
Leu	370.35 (259.24-481.45)	315.14	3.22	304.38	5.06	310.56	3.65	310.03	1.74
Lys	174.61 (122.23-227)	176.57	3.58	170.32	5.23	166.59	4.60	171.16	2.95
Met	56.29 (39.4-73.17)	57.98	5.39	56.61	5.10	56.27	3.82	56.95	1.59
Orn	153.16 (107.21-199.11)	147.10	3.51	140.90	4.95	138.27	4.93	142.09	3.19
Phe	97.20 (68.04-126.36)	89.97	4.34	86.25	5.10	88.27	3.34	88.16	2.11
Pro	456.05 (319.23-592.86)	383.32	4.05	363.86	5.27	366.56	3.54	371.24	2.84
Ser	663.61 (464.53-862.69)	541.68	8.07	491.30	8.23	492.89	8.32	508.62	5.63
Tyr	225.15 (157.6-292.69)	253.95	4.35	247.55	5.67	255.87	2.77	252.46	1.73
Val	181.33 (126.93-235.72)	102.43*	4.10	101.26*	5.45	102.63*	3.64	102.11*	0.72
C0	42.10 (29.47-54.73)	33.09	6.28	32.99	6.41	31.58	4.51	32.55	2.59
C2	30.19 (21.13-39.25)	25.19	3.79	24.60	4.83	23.69	3.35	24.49	3.08
C3	7.17 (5.02-9.32)	6.26	2.81	6.33	5.74	6.05	2.88	6.21	2.36
C4	1.39 (0.97-1.81)	1.16	4.63	1.19	5.69	1.12	3.87	1.16	2.94
C5	1.47 (1.03-1.91)	1.34	4.55	1.30	4.72	1.23	3.46	1.29	4.32
C5DC	2.22 (1.56-2.89)	1.99	7.88	2.07	6.27	2.02	5.21	2.02	1.95
C6	0.83 (0.58-1.08)	0.68	5.35	0.66	5.37	0.62	3.98	0.65	4.06
C8	1.06 (0.74-1.38)	0.80	4.58	0.82	7.09	0.74	2.16	0.79	5.05
C10	0.23 (0.16-0.3)	0.18	5.42	0.18	6.01	0.16	5.50	0.18	5.75
C12	0.60 (0.42-0.79)	0.53	8.22	0.52	8.47	0.47	5.56	0.51	6.65
C14	0.52 (0.37-0.68)	0.53	7.63	0.52	7.66	0.48	5.22	0.51	5.23
C16	6.53 (4.57-8.48)	5.50	4.86	5.60	6.85	5.26	3.88	5.45	3.13
C18	1.93 (1.35-2.51)	1.58	4.28	1.73	7.38	1.63	3.39	1.65	4.56
ASA	41.01 (28.7-53.31)	29.63	6.58	30.11	9.72	33.04	8.71	30.93	5.97
SUAC	8.70 (6.09-11.31)	5.49*	6.90	5.46*	8.83	5.48*	8.56	5.48*	0.23

* The measured levels were slightly lower than the target range, but this was determined to be acceptable (see the text for explanations).

Table 3c. Inter-day and intra-day precision (Level III)

Analytes	Control values	Day-1		Day-2		Day-3		Inter-day	
	µM	Conc. (µM)	%CV	Conc. (µM)	%CV	Conc. (µM)	%CV	Conc. (µM)	%CV
Ala	1201.31 (840.92-1561.7)	871.41	7.81	796.50*	5.34	844.69*	7.19	837.53*	4.53
Arg	315.98 (221.19-410.77)	185.88*	3.78	173.41*	3.87	176.96*	3.67	178.75*	3.59
Asp	612.90 (429.03-796.77)	519.48	8.04	470.93	8.74	482.34	8.04	490.92	5.17
Cit	320.65 (224.46-416.85)	251.87	5.88	217.03*	5.68	258.96	4.39	242.62	9.25
Glu	1594.14 (1115.9-2072.39)	1381.63	5.11	1259.91	4.68	1322.47	6.36	1321.34	4.61
Gly	1331.30 (931.91-1730.69)	1186.65	3.97	1125.87	9.07	1167.81	7.70	1160.11	2.68
Leu	608.39 (425.87-790.91)	506.41	3.40	464.22	4.39	482.74	4.44	484.46	4.37
Lys	573.13 (401.19-745.07)	569.01	4.05	510.60	4.27	521.08	6.16	533.56	5.84
Met	254.26 (177.98-330.54)	241.41	5.36	226.25	5.41	231.39	4.81	233.01	3.31
Orn	512.48 (358.74-666.23)	482.42	4.07	433.06	5.18	455.37	4.72	456.95	5.41
Phe	360.78 (252.54-469.01)	317.04	3.68	285.14	4.57	300.37	4.40	300.85	5.30
Pro	775.29 (542.7-1007.88)	670.63	4.44	591.09	4.25	615.13	4.30	625.62	6.52
Ser	1135.22 (794.66-1475.79)	835.83	8.73	799.76	8.10	832.12	8.14	822.57	2.41
Tyr	475.13 (332.59-617.66)	540.38	3.20	500.76	3.85	515.80	3.27	518.98	3.85
Val	639.76 (447.83-831.69)	359.46*	2.93	330.81*	5.47	345.97*	4.36	345.41*	4.15
C0	77.43 (54.2-100.66)	60.37	4.49	57.55	4.52	56.63	3.78	58.19	3.35
C2	55.98 (39.18-72.77)	45.66	3.77	41.92	4.58	42.47	4.34	43.35	4.65
C3	14.45 (10.12-18.79)	12.54	4.70	12.02	3.70	11.89	3.55	12.15	2.83
C4	2.83 (1.98-3.67)	2.36	3.65	2.25	5.26	2.23	5.32	2.28	2.99
C5	3.02 (2.12-3.93)	2.67	5.01	2.49	4.73	2.51	3.27	2.56	3.87
C5DC	4.91 (3.44-6.39)	4.16	6.40	3.96	6.61	3.98	5.16	4.03	2.76
C6	1.73 (1.21-2.24)	1.36	3.84	1.26	4.82	1.25	4.41	1.29	4.54
C8	2.22 (1.55-2.88)	1.63	4.84	1.55	5.15	1.49	4.13	1.56	4.24
C10	0.46 (0.32-0.6)	0.36	6.57	0.33	8.14	0.32	7.59	0.34	6.99
C12	1.21 (0.85-1.57)	1.05	3.62	0.96	6.12	0.93	4.86	0.98	6.52
C14	1.01 (0.71-1.31)	1.00	3.58	0.93	6.34	0.90	5.94	0.94	5.66
C16	12.53 (8.77-16.28)	10.40	3.36	9.79	5.32	9.50	4.87	9.90	4.64
C18	3.41 (2.39-4.43)	2.83	2.86	2.93	4.34	2.69	4.79	2.81	4.20
ASA	90.14 (63.1-117.18)	65.72	10.91	68.98	6.63	74.08	11.15	69.59	6.05
SUAC	14.40 (10.08-18.73)	10.11	5.61	9.42*	6.32	10.24	7.26	9.92*	4.45

* The measured levels were slightly lower than the target range, but this was determined to be acceptable (see the text for explanations).

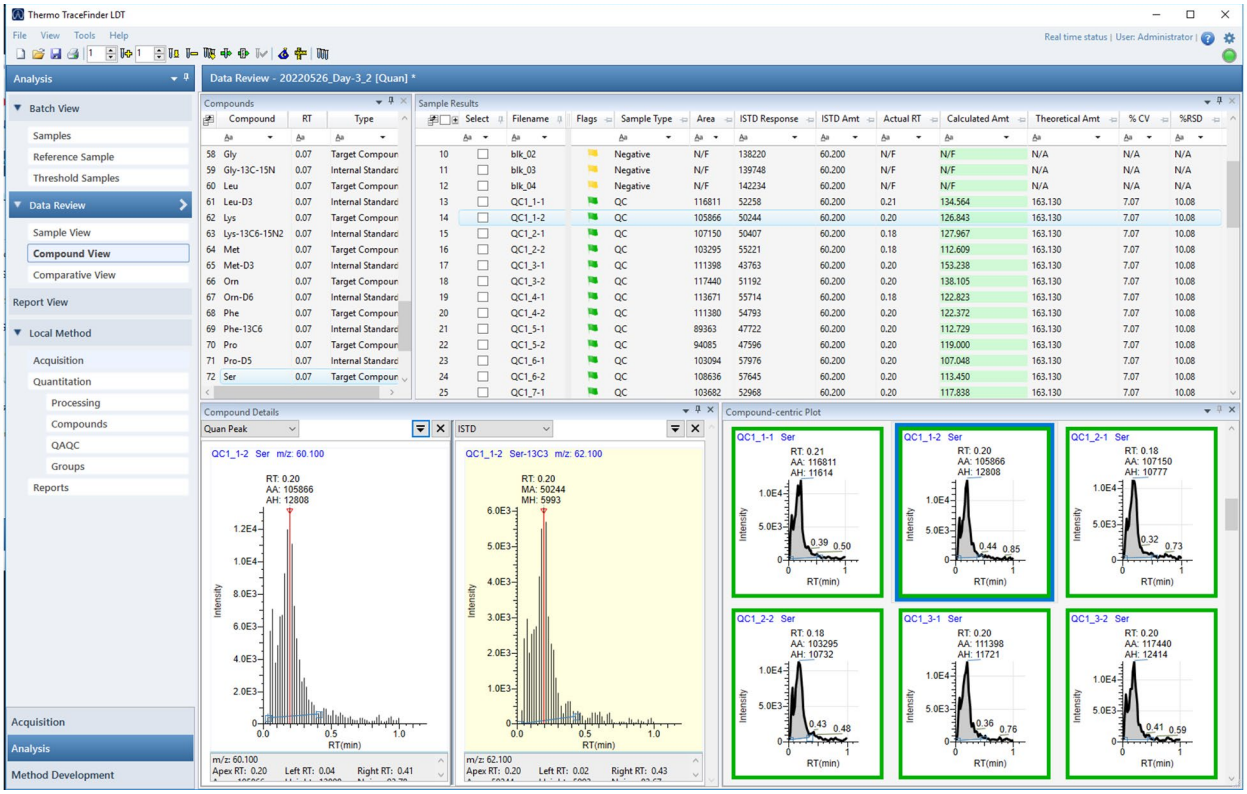


Figure 1a. TraceFinder software Compound View showing the processing results of Ser in the positive ESI mode

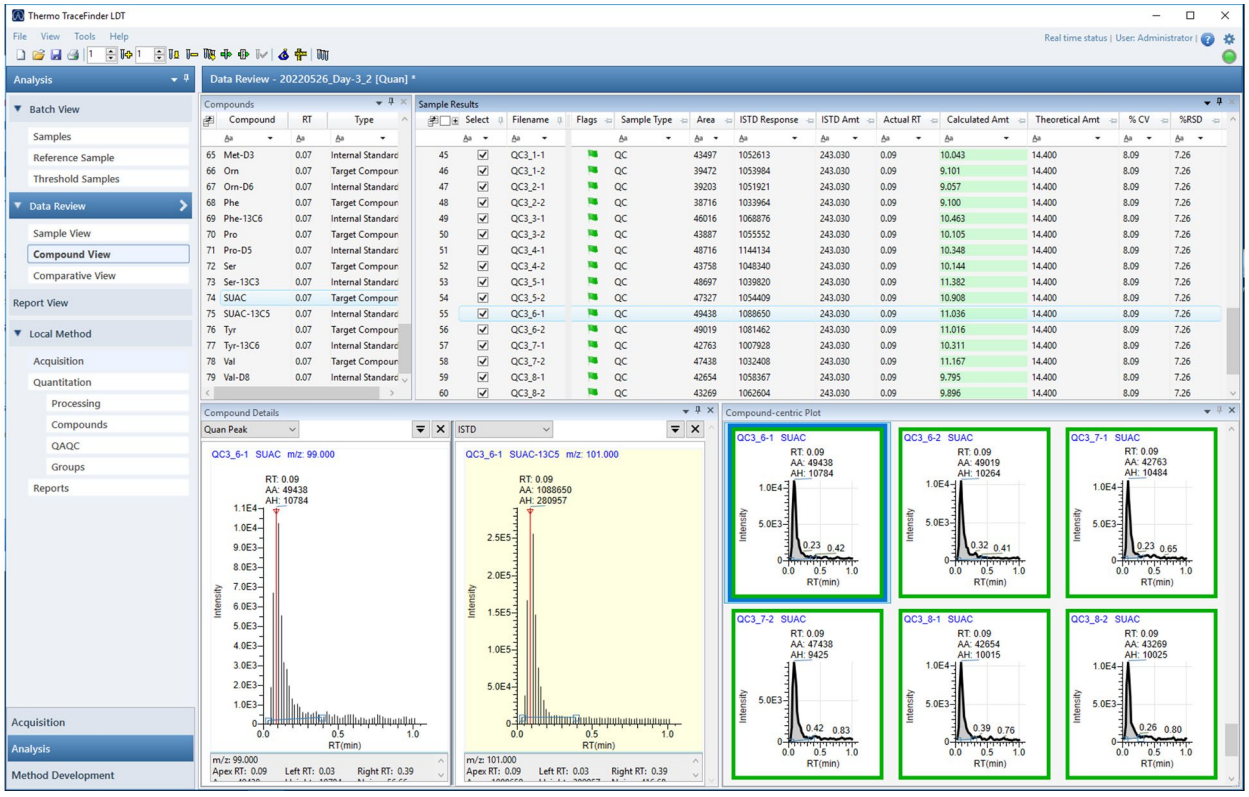


Figure 1b. TraceFinder software Compound View showing the processing results of SUAC in the negative ESI mode.

Conclusions

The reliable quantitation of 15 amino acids, 13 acylcarnitines, succinylacetone, and argininosuccinic acid in the NeoMass AAAC Plus kit was verified on a Vanquish MD HPLC and TSQ Quantis MD MS. The method met accuracy and precision requirements typically required by the state clinical laboratories performing routine primary screening for metabolic disorders in newborns.

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*Not for Clinical Diagnosis.